PROTOCOL

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED STUDY OF THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF THE PORT DELIVERY SYSTEM WITH RANIBIZUMAB IN PATIENTS WITH DIABETIC RETINOPATHY (PAVILION)**
PROTOCOL NUMBER:	GR41675
VERSION NUMBER:	4
EUDRACT NUMBER:	*Not Applicable*
IND NUMBER:	113552
NCT NUMBER:	NCT04503551
TEST PRODUCT:	Port Delivery System with Ranibizumab (RO4893594)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL:	See electronic *signature and* date stamp *on the final page of this document.*

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
4	See electronic date stamp on the final page of this document.
3	9 May 2022 (No patients treated on Version 3)
2	6 March 2021
1	2 March 2020

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Protocol GR41675 has been amended in accordance with the Update on Septum Dislodgement for Port Delivery System with ranibizumab (PDS) Studies (31 May 2022) Dear Investigator Letter to allow, in cases of septum dislodgement, a patient to receive a new implant. Because no patients were consented on Version 3 of the protocol, Version 4 would show cumulative changes from both Versions 3 and 4. While no patients were treated on Version 3 of the protocol, the protocol was amended to update the identified risks associated with PDS implant, align elements of the protocol across all clinical trials using the PDS, update the statistical analysis plan, and incorporate clarifications and additions to the study design.

Changes from Protocol GR41675, Version 4

The key changes to Version 4 of the protocol, along with a rationale for each change, are summarized as follows:

- Because septum dislodgement is an identified risk associated with PDS, the study has been updated so that, after consultation with the Medical Monitor, a patient may receive a new implant following explantation of the original implant. As a result, the following new language has been included:

  Patients must undergo new implant insertion at the time of explantation using the original incision site to place the new implant (Sections 3.1.4.3, 4.3.2.1, and 5.1.5.8).

  Patients can receive Sponsor-supplied intravitreal ranibizumab 0.5 mg in the study eye for the treatment of diabetic retinopathy prior to explantation and new implant insertion (Sections 3.1.4.3 and 4.3.2.2).

  If a patient cannot undergo re-implantation or if an anti-vascular endothelial growth factor agent other than ranibizumab is administered in the study eye, the patient must be discontinued from study treatment (as no additional refill-exchange procedures can be performed) (Section 3.1.4.3).

  If the last study visit was completed more than 4 weeks (28 days) prior to the explantation/re-implantation scheduled date, an additional visit (as an unscheduled visit) must be performed (Sections 4.3.2.1).

  After re-implantation, patients will complete post–re-implantation study visits and continue with the originally scheduled refill-exchange procedures every 36 weeks per protocol (Sections 4.3.2.1 and 5.1.1 and Appendix 4).

  Dilated binocular indirect ophthalmoscopy examinations will be performed in the study eye after a new implant has been inserted (Sections 4.5.4 and 5.1.1, Appendix 2 [Tables 1 and 2], and Appendix 3 [Table 2]).

Patients with septum dislodgement who elect not to undergo explantation or new implant insertion will be discontinued from study treatment and no additional refill-exchange procedures will be performed. These patients will be eligible to receive Sponsor-provided intravitreal ranibizumab 0.3 mg treatment as per local label and regulations and per clinical judgment of the investigator following consultation with Medical Monitor (Section 4.6.1).

Safety language has been updated to help manage patients undergoing new implant insertion in case of septum dislodgement (Sections 5.1.1, 5.1.5.2, and 5.1.5.8).

A new schedule of activities has been added for patients undergoing new implant insertion following implant removal (Appendix 4; subsequent appendices have been renumbered).

- The general exclusion criterion on the duration for pregnant or breastfeeding, or intending to become pregnant has been extended to 3 months (Section 4.1.2.1).
- For patients in the comparator arm who are on anticoagulant or antiplatelet therapy, the timepoint to which they need to temporarily interrupt these medications has been updated to reflect their Week 64 implant visit (Section 4.4.1).

Changes from Protocol GR41675, Version 3

The key changes to Version 3 of the protocol, along with a rationale for each change, are summarized as follows:

- Background on the PDS has been revised to include the results from the completed Phase III Study GR40548 (Archway) and to reflect the United States Food and Drug Administration's approval of the PDS in patients with neovascular age-related macular degeneration (Section 1.3).
- Septum dislodgement has been identified as a risk associated with the PDS. Appropriate guidance on the diagnosis and management of these cases has been added (Sections 1.4, 4.5.4, 5.1.2.8, and 5.1.5.8).
- Septum dislodgement has been added as an anticipated serious adverse device effect (immediately reportable to the Sponsor [Section 5.2.2.3])
- The following updates have been made to the study objectives and endpoints:
  - The secondary efficacy objective has been modified to the rate of patients developing a $\geq$3-step worsening from baseline on the ETDRS-DRSS through Week 52 (Sections 2.1.2 and 6.4.2).
  - The proportion of patients with absence of intraretinal fluid, subretinal- fluid or both (as measured in the central 1mm subfield) over time has been added as a secondary efficacy objective (Sections 2.1.2 and 6.4.2).
  - Patient treatment and experience objectives to include proportion of patients who report preferring PDS treatment to intravitreal ranibizumab treatment, as measured by the PPPQ at Week 52 (Section 2.1.2).
  - The revision of pharmacokinetic (PK) endpoints to include maximum serum concentrations as part of the estimand PK parameter (Section 2.3).

  - To assess the prevalence of neutralizing antibodies at baseline and incidence of neutralizing antibodies during the study, new immunogenicity objectives have been added (Section 2.4).
  - The exploratory immunogenicity objective has been revised to include assessment of neutralizing antibodies (Section 2.4).
  - The biomarker objectives have been changed to exploratory biomarker objectives (Section 2.5).
  - An exploratory device and procedure-experience objective was added to assess the incidence of device deficiencies (Section 2.7).
- The procedural and device aspects of the PDS require the differentiation and subsequent reporting of adverse events that are potentially related to device or procedure as per the International Organization for Standardization (ISO®) 14155:2020 and the E.U. Medical Device Regulation (MDR) (2017/745):
  - Device and procedure-related safety objectives are now included (Section 2.7)
  - Rationale for device and procedure assessments has been added (Section 3.3.7)
  - Investigational device and handling accountability has been added (Section 4.3.3)
  - The safety parameters and definitions have been updated to include device and procedure-related parameters (Section 5.2)
  - Reporting requirements for medical devices have been updated to clarify the medical devices used in this study and updated instruction for investigators on reporting of device deficiencies and study drug complaints (Section 5.4.4).
  - Language has been added to highlight study compliance with ISO 14155:2020 and E.U. MDR 2017/745 (Section 8.1).
  - Guidelines for the investigator on categorization of adverse events related to device or procedure have been added (Appendix 18).
- The recommended management of patients with conjunctival retraction or conjunctival erosion, conjunctival bleb, endophthalmitis, and device dislocation have been updated with the most recent guidance (Sections 5.1.5.4, 5.1.5.5, 5.1.5.6, and 5.1.5.7).
- To align the dose interruption, study treatment discontinuation, or study discontinuation criteria (Table 1) guidance across all clinical trials using the PDS, the following changes have been made:
  - Inclusion of interruption criteria for observed abnormalities in the conjunctiva and dose interruption criteria for local or systemic infection to reflect the most recent guidance
  - Revision of the description of the implant category to include observed damage to implant components

- Removal of the dose interruption requirement for concomitant use of IV corticosteroids during the study as it is no longer deemed necessary (Section 5.1.5.2)

- The recommended management of patients with endophthalmitis has been updated to include conjunctiva management and early detection with surgical repair. Additionally, as previously communicated in GR41675 Protocol Version 2, Clarification Letter #1 (15 December 2021), vancomycin concentration used for implant flush has been updated to 100 µL vancomycin (1.0 mg/0.1 mL) (Section 5.1.2.6).

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

- Language has been added to clarify that the PDS implant is intended to remain permanently in the eye unless explanted for medical reasons (Section 1.4).
- The impact of the coronavirus 2019 (COVID-19) pandemic on the benefit-risk assessment of the study has been added (Section 1.4).
- The responsibilities of the investigator and the role of the Medical Monitor during study conduct have been clarified (Sections 3.1.4, 5.1.5, 5.4.3.1, Appendix 2, and Appendix 3).
- The temperature range for storing implant, insertion tool, initial fill needle, refill needle, and explant tool has been updated (Section 4.3.1.1).
- Language has been added to clarify that one or more representatives from the Sponsor or an affiliate to the Sponsor may be present during the study-specific PDS surgeries or procedures (initial filing of implant, implant insertion, refill-exchange, and/or explantation) (Section 4.3.2.1).
- Text has been added to clarify supplemental treatment within the first 3 months after implant insertion in patients in the compartor arm (Section 4.3.2.3).
- Language has been added to indicate that the study site is responsible for maintaining records of investigational medicinal product (IMP) delivery to the site, IMP inventory at the site, IMP use by each patient, and destruction or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol (Section 4.3.4).
- A description of IMP accountability has been added to indicate that sites can confirm that appropriate temperature conditions have been maintained during IMP transit either by time monitoring (using shipment arrival date and time) or temperature monitoring (Section 4.3.4).
- Text has been added to indicate that there is no evidence of drug-drug interaction between ranibizumab and SARS-CoV-2 vaccines to date and the administration of the SARS-CoV-2 vaccines should be documented on the appropriate electronic Case Report Form (eCRF; Section 4.4).
- Text has been added to clarify that yttrium aluminum garnet (YAG) laser capsulotomy and selective laser trabeculoplasty are permitted in the study eye (Section 4.4.1).

- To align with the most recent guidance, language was updated to clarify when periocular corticosteroids and suprachoroidal corticosteroids are prohibited in the study eye (Section 4.4.2).
- Language has been added to include implant photographs obtained after application of topical fluorescein to the surface of the eye over the implant to monitor conjuctiva (Section 4.5.5).
- Language has been revised to permit the collection of optional AS-OCT angiography (AS-OCTA) images from study patients at selected sites or per investigator discretion. (Section 4.5.5).
- Text has been added to include intraocular fluids as contents to be collected with the explanted implant (Section 4.5.6).
- The Emergency Medical Contacts have been updated to include the revised secondary Medical Monitor (Section 5.4.1).
- The reporting period in Informed Consent Form if a patient becomes pregnant has been updated (Section 5.4.3.1). This section also updated process of handling pregnancies in female patients if it is medically necessary, as per investigator's judgement and following discussion with the Medical Monitor.
- Additional recent revelant journal publications have been added (Section 10).
- Nomenclature has been updated in the Schedule of Activities from "adverse events, adverse device effects, and device deficiencies" (Appendices 2–5).
- An optional serum PK sample has been added to the unscheduled visit schedule of assessments (Appendix 5). Patients who elect to provide such samples must sign the Optional Sample Informed Consent.
- Instructions have been added to clarify which assessments must be repeated if refill-exchange must be reattempted prior to the next scheduled visit (Appendices 2 and 3) and if supplemental treatment is delayed to allowable window (Appendix 6).

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED STUDY OF THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF THE PORT DELIVERY SYSTEM WITH RANIBIZUMAB IN PATIENTS WITH DIABETIC RETINOPATHY (PAVILION)**
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MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED STUDY OF THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF THE PORT DELIVERY SYSTEM WITH RANIBIZUMAB IN PATIENTS WITH DIABETIC RETINOPATHY (PAVILION)**
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EUDRACT NUMBER:	*Not Applicable*
IND NUMBER:	113552
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TEST PRODUCT:	Port Delivery System with Ranibizumab (RO4893594)
PHASE:	III
INDICATION:	Diabetic retinopathy
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

This study is a multicenter, randomized, visual assessor–masked study in patients with diabetic retinopathy (DR) without center-involved diabetic macular edema (DME) to evaluate the efficacy, safety, and pharmacokinetics of ranibizumab 100 mg/mL delivered via the PDS every 36 weeks (Q36W) relative to the comparator arm. Specific objectives and corresponding endpoints for the study are outlined below.

Efficacy Objectives

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the superior efficacy of ranibizumab 100 mg/mL delivered via the PDS Q36W compared with observation on the basis of the following endpoint measured in the study eye:

- Proportion of patients with a ≥2-step improvement from baseline on the ETDRS Diabetic Retinopathy Severity Scale (ETDRS-DRSS) at Week 52

Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of ranibizumab 100 mg/mL delivered via the PDS Q36W relative to the comparator arm on the basis of the following endpoints measured in the study eye:

- Rate of patients developing a vision-threatening complication (defined as proliferative DR (PDR), anterior segment neovascularization (ASNV), or center-involved DME [CI-DME] [defined as central subfield thickness [CST] ≥325 µm on spectral-domain optical coherence tomography [SD-OCT]) through Week 52
- Rate of patients developing PDR or ASNV through Week 52
- Rate of patients developing CI-DME through Week 52
- Rate of patients developing a ≥2-step worsening from baseline on the ETDRS-DRSS through Week 52
- Proportion of patients with a ≥3-step improvement from baseline on the ETDRS-DRSS at Week 52

- *Rate* of patients *developing* a ≥3-step worsening from baseline on the ETDRS-DRSS *through* Week 52
- Proportion of patients with a ≥2-step improvement from baseline on the ETDRS-DRSS over time
- Proportion of patients with a ≥3-step improvement from baseline on the ETDRS-DRSS over time
- Time to first development of either PDR, ASNV, or CI-DME
- Time to first development of PDR or ASNV
- Time to first development of CI-DME
- Time to first development of a ≥2-step worsening from baseline on the ETDRS-DRSS
- Time to first development of a ≥3-step worsening from baseline on the ETDRS-DRSS
- Change from baseline in BCVA as measured on the ETDRS chart over time
- Proportion of patients who lose <15, <10, and <5 letters in BCVA from baseline over time
- Proportion of patients with a BCVA score of 69 letters (20/40 approximate Snellen equivalent) or better over time
- Change from baseline in CST as measured on SD-OCT over time
- Change from baseline in total macular volume as measured on SD-OCT over time
- *Proportion of patients with absence of intraretinal fluid, subretinal fluid or both (as measured in the central 1 mm subfield) over time*
- Proportion of patients who do not undergo supplemental treatment with intravitreal ranibizumab within each refill-exchange interval
- *Proportion of patients who report preferring PDS treatment to intravitreal ranibizumab treatment, as measured by the PPPQ at Week 52*

Exploratory Efficacy Objective

The exploratory efficacy objectives for this study are the following:

- To evaluate the efficacy of ranibizumab 100 mg/mL delivered via the PDS Q36W compared with observation on the basis of the following endpoints:
  - Change from baseline in total area of retinal non-perfusion and retinal ischemia over time
  - Time to first vitrectomy for complications of PDR
  - Time to first *panretinal photocoagulation (PRP)*
  - Proportion of patients that receive supplemental treatment after the PDS implant insertion and number of supplemental treatments patients receive
  - Proportion of patients in the comparator arm that receive an intravitreal ranibizumab 0.5 mg injection and the number of intravitreal treatments patients receive prior to Week 52
- To evaluate advanced analytics tools (e.g., artificial intelligence-based tools) to predict progression to visual threatening presentations of DR

Safety Objectives

The safety objective for this study is to evaluate the safety and tolerability of ranibizumab 100 mg/mL delivered via the PDS on the basis of the following endpoints:

- Incidence and severity of ocular adverse events
- Incidence and severity of non-ocular adverse events
- Incidence, severity, and duration of adverse events of special interest, including ocular adverse events of special interest
- Incidence, severity, and duration of ocular adverse events of special interest during the postoperative period (≤37 days after initial implant insertion) and follow-up period (>37 days after implant insertion surgery)

The device safety objectives for this study are to evaluate the device and *procedure-related* safety on the basis of the following endpoints:

- Incidence and severity of adverse device effects
- Incidence, causality, severity, and duration of anticipated serious adverse device effects

Pharmacokinetic Objectives

The pharmacokinetic (PK) objective for this study is to characterize the serum PK profile of ranibizumab 100 mg/mL delivered via the PDS after the initial and subsequent refill-exchange procedures in patients with DR on the basis of the following endpoints:

- Serum concentrations of ranibizumab observed over time
- Additional estimated PK parameter values, including area under the concentration–time curve, *maximum serum concentration,* minimum serum concentration, and half-life after PDS implant insertion

The exploratory PK objectives for this study are to evaluate potential relationships between drug exposure and the efficacy and safety of ranibizumab and to characterize ranibizumab aqueous humor concentration over time delivered via the PDS on the basis of the following endpoints:

- Relationship between serum concentrations or PK parameters for ranibizumab delivered via the PDS and efficacy endpoints
- Relationship between serum concentrations or PK parameters for ranibizumab delivered via the PDS and safety endpoints
- Measured aqueous humor concentrations of ranibizumab over time

Immunogenicity Objectives

The immunogenicity objective for this study is to evaluate the immune response to ranibizumab 100 mg/mL delivered via the PDS on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) prior to study treatment and incidence of ADAs after study treatment
- *Prevalence of neutralizing antibodies at baseline and incidence of neutralizing antibodies during the study*

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs *and neutralizing antibodies* on the basis of the following endpoint:

- Relationship between ADA status and *neutralizing antibodies and* efficacy, safety, or PK endpoints

Exploratory **Biomarkers Objectives**

The exploratory biomarker objectives for this study are to identify biomarkers that are predictive of response to ranibizumab, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can provide evidence of ranibizumab activity, or can increase the knowledge and understanding of disease biology, on the basis of the following endpoints:

- Correlation between concentration of free VEGF (VEGF not in complex with ranibizumab) in aqueous humor at baseline and over time with PK and/or efficacy endpoints
- Correlation between concentration of free VEGF in aqueous humor at baseline and over time with DR progression
- Relationship between genetic variants (such as polymorphisms within the VEGF-A genetic locus) with the disease characteristics and/or response to treatment with ranibizumab
- Relationship between baseline imaging features and response to treatment with ranibizumab or other efficacy endpoints over time
- Relationship between baseline imaging features and DR progression

Patient Treatment Experience Objectives

The patient treatment experience objectives for this study are to evaluate patient treatment satisfaction. *These objectives will be evaluated by* the following endpoint:

- Mean overall treatment satisfaction as measured by the Retinopathy Treatment Satisfaction Questionnaire, status version (RetTSQs) total score at Week 52

Device and Procedure Experience Objective

The device and procedure experience objective for this study is *to* characterize the safety *(as detailed in safety objectives)* of the PDS devices and procedures *on the basis of the following endpoint:*

- *Reported incidence of device deficiencies*

STUDY DESIGN

DESCRIPTION OF STUDY

Study GR41675 is a multicenter, randomized, visual assessor–masked study in patients with DR without CI-DME to evaluate the efficacy, safety, and pharmacokinetics of ranibizumab 100 mg/mL delivered via PDS Q36W relative to the comparator arm.

OVERVIEW OF STUDY DESIGN

Approximately 160 patients with moderately severe or severe NPDR (DRSS level 47 or 53) without CI-DME will be enrolled at approximately 100 investigational sites. Patients who are naive to any treatment for DR in the study eye are eligible for screening.

During the screening period, the inclusion and exclusion criteria will be assessed and eligibility to participate in the study will be determined. Patients who are eligible to participate in the study will be randomized in a 5:3 ratio to one of two arms stratified by baseline ETDRS-DRSS level (47 vs. 53) and intraretinal or subretinal fluid status on SD-OCT (present vs. absent) as assessed at baseline by a central reading center.

The two study arms are as follows:

- **PDS Arm (n = 100):** Patients randomized to the PDS arm will receive two loading doses with intravitreal ranibizumab 0.5-mg injections before the PDS implant procedure. The first loading dose will be administered at the end of the Day 1 visit. The second loading dose will be administered at the Week 4 visit (±7 days). The PDS implant (pre-filled with ranibizumab 100 mg/mL) will be surgically inserted 1–14 days after the second loading dose and within the Week 4 visit window. Patients will undergo PDS implant refill-exchange procedures (ranibizumab 100 mg/mL) Q36W thereafter.
- **Comparator Arm** (n = 60): Patients randomized to the comparator arm will undergo study visits every 4 weeks (Q4W) for observation and comprehensive clinical monitoring for the first 60 weeks. After the observation period, patients will receive two loading doses with intravitreal ranibizumab 0.5 mg injections before PDS implant insertion surgery. The first loading dose will be administered at the end of the Week 60 visit. The second loading dose will be administered at the Week 64 visit (±7 days). The PDS implant (pre-filled with ranibizumab 100 mg/mL) will be surgically inserted 1–14 days after the second loading dose and within the Week 64 visit window. Patients will receive PDS implant refill-exchange procedures (ranibizumab 100 mg/mL) Q36W thereafter.

SCREENING

Informed consent must be administered to and signed by patients before any study-specific screening procedures are performed. Each consented patient must satisfy the eligibility criteria as applicable at screening.

As part of the screening process, color fundus photography (CFP), fluorescein angiography (FA), and SD-OCT images will be obtained. A central reading center will evaluate fundus images as appropriate to provide an objective assessment of patient eligibility.

Patients who do not meet eligibility criteria (i.e., screen-failed patients) may be eligible to repeat screening up to two times, at the investigator's discretion. At rescreening, a new screening number will be assigned to the patient through an interactive voice- or web-based response system (IxRS) and all screening assessments will be performed. Glycosylated hemoglobin (HbA_{1c}) measurements taken within 2 months prior to rescreening visit and reading-center-

accepted FA images taken within 3 months prior to rescreening can be accepted and do not have to be repeated.

If HbA1c is >12% at screening, it can be retested within the 21-day screening period, if deemed appropriate by the investigator. The most recent HbA1c test results will be considered for eligibility. The patient may proceed to randomization visit if HbA1c level is ≤12% provided that all other eligibility criteria are met.

Patients who have been screened as outlined in Protocol GR40550 (*DME* trial; Pagoda) who do not meet eligibility criteria for Pagoda trial (Study GR40550) may submit their Pagoda acquired screening images and laboratory biomarker, and other biological sample results to be used for screening *in Study GR41675* (Pavilion) within 21 days of their initial collection with the exception of *reading-center*-accepted FA images which can be submitted if taken within 3 months of the GR41675 screening visit.

RANDOMIZATION

The randomization day (Day 1) assessments will be completed according to the protocol. Once the patients are deemed eligible to participate in the study, with presence of moderately severe or severe NPDR (DRSS level 47 or 53) confirmed on CFP by the central reading center, and all inclusion and exclusion criteria are met per protocol, the patients will be randomized to either the PDS arm or the comparator arm within 21 days from the date when the first screening assessment is completed. Randomization will be stratified by ETDRS-DRSS level (47 vs. 53) and intraretinal or subretinal fluid status on SD-OCT (present vs. absent) as assessed at baseline by a central reading center.

Once patients are randomized, they will proceed with the schedule planned for each of the two study arms.

COMPARATOR-CONTROLLED STUDY TREATMENT PHASE AND PDS EXTENSION PHASE

PDS ARM

Patients randomized to the PDS arm will receive at least two loading doses with intravitreal ranibizumab 0.5 mg injections, administered at Day 1 and Week 4 visits. The first loading dose must be administered after the conclusion of the randomization visit assessments. At Week 4, patients must complete a pre-implant visit prior to the implant insertion surgery. Both visits must be completed within the Week 4 window and the PDS implant (pre-filled with ranibizumab 100 mg/mL) will be surgically inserted 1–14 days after the second loading dose (e.g., if the patient receives the second loading dose at Day 28 (Week 4), implant insertion surgery must occur no earlier than Day 29 and no later than Day 35).

If PDS implant insertion surgery cannot be completed within this required timeframe because of an extenuating circumstance, PDS implant insertion surgery may be postponed *following consultation* with *the* Medical Monitor.

Patients in the PDS arm will undergo refill-exchange procedures (ranibizumab 100 mg/mL) at Weeks 40, 76, 112, and Q36W thereafter (Visit Z refill-exchange visit) until the end of the study as outlined in the protocol.

After PDS implant insertion surgery, patients will undergo scheduled visits for safety assessments at the following times: the day immediately after the implant insertion surgery (post-implant insertion Visit 1); 7 (± 2) days after implant insertion surgery (post-implant insertion Visit 2); at the Week 8 visit (± 7 days); Q4W (± 7 days) thereafter until Week 88; and every 12 weeks (Q12W) (± 7 days) thereafter until the end of the study. Following delayed PDS implant insertion surgery, the timing of subsequent *refill-exchange* procedures will remain unchanged and should be administered as outlined in the protocol.

Patients in the PDS arm who meet specific clinical criteria (development of CI-DME or PDR/ASNV) per investigator assessment can receive supplemental treatment with intravitreal ranibizumab 0.5 mg injections per investigator's clinical judgment at any non–refill exchange study visit during the study.

COMPARATOR ARM

Patients randomized to the comparator arm will undergo study visits Q4W for observation and comprehensive clinical monitoring. Beginning at Week 60, patients will receive two loading doses with intravitreal ranibizumab 0.5 mg injections, administered at the Week 60 and

Week 64 visits. At Week 64, patients must complete a pre-implant visit prior to the implant insertion surgery. Both visits must be completed within the Week 64 window and the PDS implant (pre-filled with ranibizumab 100 mg/mL) surgically inserted 1–14 days after the Week 64 intravitreal injection.

Patients in the comparator arm will undergo a refill-exchange procedure with ranibizumab 100 mg/mL at Week 100 and Q36W thereafter (Visit Z refill exchange visit) until the end of the study as outlined in the protocol.

If PDS implant insertion surgery cannot be completed within this required timeframe because of an extenuating circumstance, the PDS implant insertion may be postponed *following consultation* with *the* Medical Monitor.

After PDS implant insertion surgery, patients will undergo scheduled study visits for safety assessments at the following times: the day immediately after the implant insertion procedure (post-implant insertion Visit 1); 7 (± 2) days after implant insertion (post-implant insertion Visit 2); at the visits at Weeks 68, 72, 76, 80, 84, and 88 (± 7 days); and Q12W (± 7 days) thereafter until the end of the study. Following delayed PDS implant insertion surgery, the timing of subsequent refill-exchange procedures will remain unchanged and should be administered as outlined in the protocol.

After randomization (Day 1) and until the Week 56 visit (i.e., the comparator-controlled study treatment phase), patients randomized to the comparator arm who meet specific clinical criteria (development of CI-DME or PDR/ASNV) per investigator assessment can be treated with supplemental intravitreal ranibizumab 0.5 mg injections. The protocol criteria must be met for the first supplemental intravitreal ranibizumab treatment; subsequent supplemental treatments in the comparator arm can be done per investigator discretion.

After the Week 64 visit (i.e., the PDS extension phase), comparator arm patients with the PDS implant who meet specific clinical criteria (development of CI-DME or PDR/ASNV) per investigator assessment can receive supplemental treatment with intravitreal ranibizumab 0.5 mg injections per investigator's discretion at any non-refill-exchange study visit during the study.

GENERAL INSTRUCTIONS FOR BOTH ARMS

Patients should attempt to make all scheduled study visits; however, if extenuating circumstances preclude a scheduled study visit, patients should return for the next scheduled study visit. If the next scheduled study visit is more than 4 weeks from the missed visit (e.g., the patient misses a study visit at Week 88 or later and the next scheduled visit will take place in 12 weeks), the patient should return within 4 weeks for a separate study visit. Following completion of the study visit, patients will continue with originally scheduled Q12W visits per protocol.

Beginning at Week 88, all patients will return Q12W for study visits and study-specific assessments. Optional study visits between each mandatory Q12W visit may be added per investigator discretion. Study visits will occur according to the schedules of activities and will continue until the patient completes participation in the study.

Patients will be contacted by site personnel 3 (±1) days after each intravitreal ranibizumab injection or refill-exchange procedure to elicit reports of eye pain, decrease in vision, unusual redness, or any other new ocular symptoms in the study eye. All patients receiving the PDS implant will also be asked to verify whether they have taken the prescribed, self-administered, post-treatment topical medications

In the event a patient's fellow eye (non–study eye) requires treatment for DR starting from the screening visit, the fellow eye may be treated per standard of care in accordance with local regulations. If the investigator chooses to treat the fellow eye with ranibizumab, the Sponsor will provide *intravitreal* ranibizumab 0.3 mg as per local label and regulations starting from the screening visit. Study eye treatment and fellow eye treatment may be administered at the same study visit. However, all study eye assessments and study eye treatment should be completed per protocol first, followed by treatment in the fellow eye.

All patients will complete a final study visit after completion of study treatment. Patients who prematurely discontinue from study treatment will be encouraged to continue participating in the study and attend as many visits as possible, with an emphasis on the Week 52 visit. Patients who cannot comply with protocol requirements, including the PDS implant procedure, may be

discontinued from the study. Patients who are prematurely discontinued from the study will complete an early termination visit.

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

Study investigators will be qualified ophthalmologists, trained in the management of retinal diseases and ocular surgery. *Study investigators performing PDS procedures* will be trained by the Sponsor to perform study-specific PDS implant insertion surgery, refill-exchange procedure, and explantation- procedures. The surgical procedures involved in the use of the investigational devices are also detailed in the PDS *instructions for use* (IFU) document. If an investigator is not able to follow the current IFU, the Sponsor may decide to intervene (e.g., pause in recruitment, re-training, or replacement of *the* investigator).

It is strongly preferred that each site has one investigator who evaluates and treats all patients, with backup investigators selected. The site may opt to have more than one investigator, but to maintain consistency in the evaluation and treatment of patients, it is strongly suggested that the same physician conduct the evaluation and treatment of each individual patient throughout the trial.

POSTPONEMENT OF PDS IMPLANT INSERTION

If PDS implant insertion surgery cannot be completed within the required timeframe (1–14 days after intravitreal ranibizumab 0.5 mg injection and within the study visit window) because of an extenuating circumstance, the PDS implant insertion may be postponed once for approximately 4 weeks *following consultation* with *the* Medical Monitor. If *the decision is to postpone insertion of the implant, then* the patient will receive an additional intravitreal ranibizumab 0.5 mg injection at the next scheduled Q4W study visit, and will then have the PDS implant (pre-filled with ranibizumab 100 mg/mL) surgically inserted 1–14 days after the intravitreal injection and within the same visit window. For example, if a patient in the PDS arm receives the additional loading dose at Day 56 (Week 8), implant insertion surgery must occur no earlier than Day 57 and no later than Day 63, or if a patient in comparator arm receives the additional loading dose at Day 476 (Week 68), implant insertion surgery must occur no earlier than Day 477 and no later than Day 483. Patients who have had their surgeries delayed by 1 month will follow the modified assessments as outlined in the protocol. If PDS implant insertion surgery cannot be completed by Week 8 (PDS arm) or Week 68 (comparator arm), the patient will be withdrawn from the study and will be required to return for an early termination evaluation visit 30 (+7) days following the last intravitreal ranibizumab injection for monitoring of all adverse events (serious and non-serious) and early termination assessments.

In cases of septum dislodgement, after consultation with the Medical Monitor, a patient may receive a new implant following explantation of the original implant. Patients must undergo new implant insertion at the time of explantation using the original incision site to place the new implant. If clinically indicated, upon consultation with the Medical Monitor, the patient can receive Sponsor-supplied intravitreal ranibizumab 0.5 mg in the study eye for the treatment of DR prior to explantation and new implant insertion. If a patient cannot undergo re-implantation or if an anti-VEGF agent other than ranibizumab is administered in the study eye, the patient must be discontinued from study treatment (as no additional refill-exchange procedures can be performed)

Internal Safety Monitoring

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

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

Independent Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will monitor safety on an ongoing basis. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines the committee's roles and responsibilities. The iDMC will meet approximately every 6 months (frequency adjustable as required) to evaluate unmasked safety data (including significant decreases in BCVA), which will be prepared for the committee by an independent Data

Coordinating Center (iDCC). The iDMC will provide recommendations to the Sponsor's Data Review Board (DRB) Chair as described in the iDMC Charter. On behalf of the Sponsor, the DRB Chair will accept or reject the recommendations.

Full details regarding the roles and responsibilities of the iDMC will be provided in the charter.

A nominal type I error penalty of 0.0001 (two-sided) will be taken for each time the iDMC reviews unmasked data prior to the formal analysis of the primary efficacy endpoint. At the time of the primary *efficacy endpoint* analysis, it is estimated that four interim data reviews will have been conducted by the iDMC; therefore, efficacy analyses will be performed at a significance level of 0.0496. The actual adjustment will depend on the actual number of iDMC meetings.

Number of Patients

Approximately 160 patients will participate in this study.

TARGET POPULATION

Inclusion Criteria

General Inclusion Criteria

Patients must meet the following general inclusion criteria for study entry:

- Ability and willingness to provide signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability and willingness to comply with the study protocol and to undertake all scheduled visits and assessments, in the investigator's judgment
- Documented diagnosis of diabetes mellitus (Type 1 or Type 2), as defined by the American Diabetes Association or per WHO criteria and
  - Current regular use of insulin for the treatment of diabetes

    and/or
  - Current regular use of anti-hyperglycemic agents for the treatment of diabetes
- HbA_{1c} level of ≤ 12% within 2 months prior to screening or at screening

  - *HbA1c can be retested within the 21-day screening period with the most recent results considered for eligibility.*
- Willingness to adhere to recommendations/measures provided by their endocrinologist or primary care physician to aim for the best possible metabolic control during participation in the study
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for at least *3 months* after the final intravitreal injection of ranibizumab or 1 year after the final refill-exchange of ranibizumab.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

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

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

Ocular Inclusion Criteria for Study Eye

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

- Moderately severe or severe NPDR (ETDRS-DRSS level 47 or 53) as assessed by the investigator and confirmed by the central reading center
- BCVA of ≥ 69 letters (20/40 approximate Snellen equivalent or better), using the ETDRS protocol at the initial testing distance of 4 meters
- Sufficiently clear ocular media and adequate pupillary dilatation to allow for analysis and grading by the central reading center

Exclusion Criteria

General Exclusion Criteria

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

- Currently untreated diabetes mellitus or previously untreated patients who initiated anti-diabetic medication or insulin within 3 months prior to randomization
- History of allergy or hypersensitivity to fluorescein or to any study-assessment or study treatment–related mandatory ingredients (e.g., disinfectants, anesthetics, etc.) that is not amenable to treatment
- Active cancer within the past 12 months, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or prostate cancer with a Gleason score of ≤6 and a stable prostate-specific antigen for >12 months
- Current systemic treatment for a confirmed active systemic infection
- Renal failure requiring renal transplant, hemodialysis, or peritoneal dialysis, or anticipated to require hemodialysis or peritoneal dialysis at any time during the study
- History of other disease, other non-diabetic metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a condition that contraindicates the use of ranibizumab or surgical placement of the PDS implant; that might affect interpretation of the results of the study; or that renders the patient at high risk for treatment complications in the opinion of the investigator or Sponsor
- Uncontrolled blood pressure (defined as systolic >180 mmHg and/or diastolic >110 mmHg while a patient is at rest) at screening

  If a patient's initial measurement exceeds these values, a second reading may be taken 30 or more minutes later. If the patient's blood pressure must be controlled by antihypertensive medication, the patient may become eligible if medication is taken continuously for at least 30 days.
- Cerebrovascular accident or myocardial infarction within 6 months prior to randomization
- Atrial fibrillation diagnosis or worsening within 6 months prior to randomization
- Use of any systemic anti-VEGF agents
- Participation in an investigational trial that involves treatment with any drug or device (with the exception of vitamins and minerals) within 6 months prior to randomization
- Administration of systemic pro-angiogenic treatments, such as VEGF-based therapies for peripheral or coronary ischemia (e.g., limb ischemia or myocardial infarction) within 6 months or 5 elimination half-lives
- Use of antimitotic or antimetabolite therapy within 30 days or 5 elimination half-lives
- Requirement for continuous use of any medications and treatments indicated in the Prohibited Therapy section of the protocol

- Pregnant or breastfeeding, or intending to become pregnant during the study treatment period and for at least *3 months* after the final intravitreal injection of ranibizumab or 1 year after the final refill-exchange of ranibizumab

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

Ocular Exclusion Criteria for Study Eye

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

- ETDRS-DRSS level other than level 47 or 53
- Presence of CI-DME (defined as CST ≥325 μm)
- Tractional retinal detachment or pre-retinal fibrosis
- Clinically significant abnormalities of the vitreous-retinal interface involving the macular area or disrupting the macular architecture, such as vitreous-retinal traction or epiretinal membrane (assessed by the investigator and confirmed by the central reading center)
- History of macular hole (Stage 3 or 4)
- Active rubeosis
- Active intraocular inflammation (grade trace or above)
- Any intravitreal anti-VEGF treatment at any time prior to randomization
- Any use of medicated intraocular implants, including Ozurdex® or Iluvien® implants, at any time prior to randomization
- Any intravitreal corticosteroid treatment at any time prior to randomization
- Any periocular (e.g., subtenon) corticosteroid treatment at any time prior to randomization
- Any PRP at any time prior to randomization
- Any macular laser photocoagulation (such as micropulse and focal or grid laser) at any time prior to randomization
- Retinal tears or peripheral retinal breaks, diagnosed within 3 months prior to randomization
- History of rhegmatogenous retinal detachment
- History of glaucoma-filtering surgery, tube shunts, or microinvasive glaucoma surgery
- Uncontrolled ocular hypertension or glaucoma (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 the investigator determines may require a glaucoma-filtering surgery during a patient's participation in the study
- Intraocular surgery (including cataract surgery) within 3 months prior to randomization
- History of corneal transplant
- History of pars plana vitrectomy
- Previous intraocular device implant insertion, unless it is a posterior chamber intraocular lens
- Aphakia or absence of the posterior capsule

  Previous violation of the posterior capsule is also an exclusion criterion unless it occurred as a result of yttrium-aluminum garnet laser posterior capsulotomy in association with prior, posterior chamber intraocular lens implant insertion.
- Spherical equivalent of the refractive error demonstrating more than 8 diopters of myopia

  For patients who have undergone prior refractive or cataract surgery in the study eye, preoperative refractive error that exceeds 8 diopters of myopia is an exclusion criterion.
- Diagnosis of concurrent or previous retinal diseases other than DR that can lead to macular edema

- Any concurrent ocular condition (e.g., cataract, epiretinal membrane) that would require surgical intervention during the study to prevent or treat visual loss that might result from that condition
- Any concurrent ocular condition (e.g., amblyopia, strabismus) that may affect interpretation of study results
- History of other ocular diseases that gives reasonable suspicion of a disease or condition that contraindicates the use of ranibizumab, that might affect interpretation of study results, or that renders the patient at high risk for treatment complications

Ocular Exclusion Criteria for Either Eye

Patients who meet any of the following exclusion criteria for either eye will be excluded from study entry:

- Suspected or active ocular or periocular infection (e.g., infectious conjunctivitis or endophthalmitis)
- Any history of uveitis (e.g., idiopathic, drug-associated or autoimmune-associated uveitis)

END OF STUDY

The end of the study is defined as the date when the last patient in the study completes their final study visit.

LENGTH OF STUDY

The duration of this study will depend on health authority approval of the PDS for this indication, as well as Sponsor decision. In the event the PDS receives health authority approval for this indication prior to 112 weeks after the last patient is randomized in this study, the Sponsor may request completion of the final visit prior to this date.

In addition, the Sponsor may decide to terminate the study at any time.

INVESTIGATIONAL MEDICINAL PRODUCTS

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

RANIBIZUMAB USED IN IMPLANT (INITIAL FILL AND REFILL-EXCHANGE)

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

RANIBIZUMAB FOR INTRAVITREAL INJECTION

Ranibizumab for intravitreal injection will be supplied by the Sponsor and is formulated as a sterile, colorless to pale yellow solution.

STATISTICAL METHODS

PRIMARY ANALYSIS

Efficacy analyses will be based on the *ITT* population comprising all patients who are randomized and receive the assigned study treatment (PDS or comparator) with patients grouped according to the treatment *assigned at randomization* (patients who receive the PDS implant before Week 52 will be included in the PDS arm).

Unless otherwise noted, analyses of efficacy outcome measures will be stratified by the randomization stratification factors (ETDRS-DRSS level [47 vs. 53] and intraretinal or subretinal fluid status on SD-OCT [present vs. absent] as assessed at baseline by a central reading center) as recorded in IxRS.

A nominal type I error penalty of 0.0001 (two-sided) will be taken for each time the iDMC reviews unmasked data prior to the primary analysis. At the time of the primary analysis, it is estimated that four interim data reviews will have been conducted by the iDMC; therefore, efficacy analyses will be performed at a significance level of 0.0496. The actual adjustment will depend on the actual number of iDMC reviews.

In addition to p-values for statistical tests, the estimates and CIs will be provided for the mean (for continuous variables) or proportion (for binary variables) for each treatment group and the difference in means or proportions between two treatment groups. All CIs will be two-sided and at the 95.04% level.

DETERMINATION OF SAMPLE SIZE

Patients will be randomly allocated in a 5:3 ratio to the PDS arm or the comparator arm.

The primary endpoint is the proportion of patients with a ≥ 2-step improvement from baseline on the ETDRS-DRSS at Week 52. A sample size of 160 patients will provide over 99% power to demonstrate an at least 35% absolute improvement in proportion of patients with a ≥2-step improvement on ETDRS-DRSS at Week 52 under the following assumptions:

- An achievement of a ≥2-step improvement on the ETDRS-DRSS at Week 52 in 15% of patients in the comparator arm (Eylea® U.S. Package Insert)
- Fisher's exact test
- A 4.96% two-sided type I error rate (after adjustment for planned interim data reviews conducted by the iDMC prior to analysis of the primary efficacy endpoint)
- A 15% dropout rate by Week 52

In case the 15% dropout rate by Week 52 is deemed under-estimated during the study enrollment period, the sample size may be increased accordingly based on a revised dropout rate estimate.

INTERIM ANALYSES

Interim safety analyses will be performed by the iDCC periodically (approximately every 6 months) and will be reviewed by the iDMC. Interim efficacy or futility analyses are not planned.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
AS-OCT	*anterior segment optical coherence tomography*
AS-OCTA	*anterior segment optical coherence tomography angiography*
ASNV	anterior segment neovascularization
BCVA	best-corrected visual acuity
CFP	color fundus photography
CI-DME	center-involved diabetic macular edema
CMH	Cochran–Mantel–Haenszel
CST	central subfield thickness
DME	diabetic macular edema
DR	diabetic retinopathy
DRB	Data Review Board
DRSS	Diabetic Retinopathy Severity Scale
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ETDRS	*Early Treatment Diabetic Retinopathy Study*
FA	fluorescein angiography
FP	*fundus photography*
HbA_{1c}	glycosylated hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IFU	*Instructions for use*
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IOP	intraocular pressure
IRB	Institutional Review Board
ISO	International Organization for Standardization
IxRS	interactive voice or web-based response system
MDR	*Medical Device Regulations*
MMRM	mixed-effect model for repeated measures
MRI	magnetic resonance imaging
nAMD	neovascular age-related macular degeneration

Abbreviation	Definition
NPDR	nonproliferative diabetic retinopathy
NSAID	nonsteroidal anti-inflammatory drug
OCT	optical coherence tomography
PD	pharmacodynamic
PDR	proliferative diabetic retinopathy
PDS	Port Delivery System with ranibizumab
PDS IFU	PDS Instruction for Use
PK	pharmacokinetic
PPPQ	PDS Patient Preference Questionnaire
PRP	panretinal photocoagulation
PVD	posterior vitreous detachment
Q4W	every 4 weeks
Q12W	every 12 weeks
Q36W	every 36 weeks
RBR	Research Biosample Repository
RetTSQs	Retinopathy Treatment Satisfaction Questionnaire, status version
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory coronavirus 2
SD-OCT	spectral-domain optical coherence tomography
ULN	upper limit of normal
UWF™	ultra-widefield
VA	visual acuity
VEGF	vascular endothelial growth factor
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON DIABETIC RETINOPATHY

Diabetic retinopathy (DR) can be a chronic and debilitating retinal vascular disease secondary to diabetes mellitus and is a leading cause of vision loss globally (Cheung et al. 2010; Lee et al. 2015). Diabetes mellitus is estimated to affect 425 million people worldwide, and its prevalence is expected to grow to 629 million by 2045 (International Diabetes Federation 2017). DR affects over one-third of patients with diabetes, and one-third of them experience vision-threatening presentations such as proliferative DR (PDR) or the presence of diabetic macular edema (DME) (Yau et al. 2012; Lee et al. 2015).

The severity of DR is typically assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (DRSS), which has been well established for the objective quantification of retinopathy severity based on color fundus photographs (ETDRS 1991a, 1991b). The ETDRS-DRSS includes 13 score levels, ranging from the absence of retinopathy to PDR, including neovascularization and/or vitreous/preretinal hemorrhage. A ≥1-step worsening on the ETDRS-DRSS is associated with a 3- to 4-fold risk of developing clinically significant DME and a high likelihood of vision loss over a 4-year period (Klein et al. 2001). Likewise, both ≥2- and ≥3-step worsenings on the ETDRS-DRSS have been associated with an increased risk of subsequent vision loss due to DR complications over time.

DR is strongly associated with elevated intraocular levels of vascular endothelial growth factor (VEGF), which mediates an increase in vessel permeability and loss of pericytes, consequent to hypoxia-mediated release of proangiogenic, hyperpermeability, and proinflammatory mediators (Antonetti et al. 1999; Boyer et al. 2013; Cohen and Gardner 2016). This has led to the development and clinical success of VEGF inhibitors in treating DR and its vision-threatening complications (Antonetti et al. 2012; Stitt et al. 2016), greatly improving visual outcomes in this challenging condition (Bressler et al. 2017; Krick and Bressler 2018).

Existing, approved therapies for DR with or without DME in the United States include ranibizumab and aflibercept. Randomized controlled clinical trials of anti-VEGF therapy in patients with DR with DME showed continued visual acuity and DME improvement over time. Improvement of at least 2 steps in DR severity was also observed at 2 years among study patients receiving anti-VEGF therapy for DME (Protocol I, RIDE [FVF4168g] and RISE [FVF4170g], VIVID, VISTA, BOLT, Protocol T, Protocol S). Ad hoc analysis of ranibizumab RIDE and RISE studies showed greatest improvement in the DRSS level in patients with moderately severe or severe nonproliferative DR (NPDR) (DRSS level of 47 or 53) (Wykoff et al. 2018). By Month 12, more than 75% of patients with a baseline DRSS level of 47 or 53 demonstrated a ≥2-step regression in DR severity following anti-VEGF therapy (Wykoff et al. 2018).

Additional options for the treatment of advanced DR include panretinal photocoagulation (PRP) and vitrectomy. However, PRP and vitrectomy may lead to adverse effects, including peripheral visual field loss, dyschromatopsia, impaired night vision, decreased contrast sensitivity, retinal breaks, cataract progression, and reduced central acuity from exacerbation of macular edema.

Progression of DR leads to subsequent vision loss due to DR complications, including DME, retinal detachment, and vitreous hemorrhage, and has a significant impact on the patient's quality of life. Patients with worsening vision due to DR show increased reliance on services, assistive devices, and caregiving (Schmier et al. 2009; Gabrielian et al. 2010; Mazhar et al. 2011; Willis et al. 2017). To achieve optimal outcomes in the absence of validated predictive biomarkers of treatment frequency, the standard anti-VEGF treatment regimens for DR with or without DME, still rely on frequent office monitoring visits and place a substantial burden on patients, caregivers, and healthcare providers (Dugel et al. 2016; Blinder et al. 2017; Wecker et al. 2017; Fong et al. 2018; Holekamp et al. 2018; Weiss et al. 2018).

1.2 BACKGROUND ON RANIBIZUMAB

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

The pivotal Phase III studies (RIDE [FVF4168g] and RISE [FVF4170g]), which studied the safety and efficacy of intravitreal ranibizumab injections in patients with DME, demonstrated significant and well-maintained visual acuity outcomes with monthly intravitreal ranibizumab 0.3-mg and 0.5-mg injections for up to 3 years (Nguyen et al. 2012; Brown et al. 2013). Additionally, the RIDE and RISE studies demonstrated that intravitreal ranibizumab reduced the risk of DR progression in eyes with DME, and many ranibizumab-treated eyes experienced improvement in DR severity (Ip et al. 2012). Patients receiving ranibizumab were significantly more likely to improve by ≥2 or ≥3 steps on the ETDRS at Month 24 compared with the sham group. Improvements in DR severity were maintained in patients after switching from ranibizumab monthly to an individualized ranibizumab 0.5 mg PRN dosing regimen (Boyer et al. 2015; Sun et al. 2019). Moreover, in Protocol S (conducted by the Diabetic Retinopathy Clinical Research Network), ranibizumab has been shown to have clinically meaningful improvement on DR severity as measured by a ≥3-step improvement from baseline in ETDRS-DRSS in both eyes with and without baseline DME at 1 and 2 years in patients with PDR (Gross et al. 2015).

Current Lucentis® U.S. prescribing information supports monthly intravitreal injection of ranibizumab 0.3 mg for treatment of DR and of DME.

Refer to the PDS Investigator's Brochure for details on nonclinical and clinical studies with ranibizumab via intravitreal injection.

1.3 BACKGROUND ON THE PORT DELIVERY SYSTEM WITH RANIBIZUMAB

The Port Delivery System with ranibizumab (PDS) is *a* drug delivery *technology* that allows physicians to use ranibizumab with a continuous delivery profile without altering its chemistry. It consists of an intraocular implant, four ancillary devices (initial fill needle, insertion tool assembly, refill needle, and explant tool), and a customized formulation of ranibizumab tailored for continuous delivery.

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

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

Prior to this *protocol amendment (Version 3) for this* study, the efficacy, safety, and treatment frequency of PDS administration ha*ve* been assessed in neovascular age-related macular degeneration (nAMD) in one Phase I *study* (FH-1.2), one Phase II *study* (GX28228 [Ladder]), and *one pivotal* Phase III *study (*GR40548 *[*Archway*]). Assessments are ongoing for nAMD in a global, Phase IIIb study (WR42221 [Velodrome]), an* open-label extension trial *(*GR40549 *[*Portal*]), and a Phase IIIb/IV open-label study (ML43000 [Belvedere]). Additionally, the efficacy, safety, and treatment frequency of PDS administration are being assessed in DME (GR40550 [Pagoda]).* For additional details about these studies, see the PDS Investigator's Brochure.

The results of the Phase II Ladder trial suggest that the PDS provides durable, effective treatment and that the optimized PDS implant insertion and refill-exchange procedure are generally well tolerated by patients with nAMD. In particular, for the PDS 100 mg/mL arm, the median time to the first *meeting* refill-exchange *criteria* was 15.*8* months, 80% of patients went ≥6 months until the first refill-exchange; and best-corrected visual acuity (BCVA) and anatomic outcomes were comparable to those with monthly intravitreal ranibizumab injections (Campochiaro et al. 2019). In general, the systemic safety profile

of PDS treatment was comparable with monthly intravitreal ranibizumab 0.5 mg injection treatment.

Study GR40548 (Archway) was a Phase III, randomized, multicenter, open-label (visual assessor-masked), active-comparator study designed to assess the efficacy, safety, and pharmcokinetics of ranibizumab 100 mg/mL every 24 weeks (Q24W) delivered via the PDS compared with monthly intravitreal ranibizumab 0.5 mg injections in patients with nAMD. The study met the primary efficacy objective, showing that ranibizumab 100 mg/mL every 24 weeks delivered via the PDS was non-inferior (lower limit confidence interval [CI]: greater than –4.5 letters) and equivalent (lower limit CI: greater than –4.5 letters and upper limit CI less than +4.5 letters) to the intravitreal 0.5 mg every 4 week regimen, as measured by the change from baseline in BCVA at the average of Week 36 and Week 40. The difference in adjusted means was -0.3 letters (95.03% CI: −1.7 to 1.1). In addition, the administration of PDS 100 mg/mL Q24W was found to be non-inferior (lower limit CI: greater than –3.9 letters) to the intravitreal ranibizumab 0.5 mg Q4W regimen, as measured by the change from baseline in BCVA, at the average of Week 44 and Week 48, with a difference in adjusted means of –0.2 letters (95.03% CI: −1.8 to 1.3). The PDS implant insertion surgery and refill-exchange procedure were generally well tolerated by patients. The systemic safety of the PDS was characterized up to the Week 48 clinical cutoff date of 11 September 2020 and was comparable to intravitreal injections of ranibizumab. Overall, the PDS has a favorable benefit–risk profile (see Section 1.4).

The Port Delivery System with ranibizumab (100 mg/mL) with Q24W refill-exchange was approved by the U.S. Food and Drug Administration (FDA) on 22 October 2021 under the tradename SUSVIMO™ (ranibizumab injection) for the treatment of patients with nAMD who have previously responded to at least two intravitreal injections of a VEGF inhibitor medication. Refer to the SUSVIMO U.S. Package Insert for details.

1.4 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

As a result of the chronic, progressive nature of DR, frequent office monitoring visits are often necessary to monitor development of vision-threatening complications and to introduce an effective treatment aiming for optimal vision and anatomic gains; however, this places a substantial burden on patients and their caregivers, treating physicians, and the healthcare system (Ciulla et al. 2003; Dugel et al. 2016; Blinder et al. 2017; Wecker et al. 2017; Fong et al. 2018; Holekamp et al. 2018; Weiss et al. 2018).

The need for frequent monitoring and timely treatment represents a substantial challenge to optimal efficacy outcomes. Indeed, in clinical practice, many patients presenting DR with or without DME are treated less frequently than per the approved prescribing information and, as a consequence, experience suboptimal efficacy (Holekamp et al. 2018; Maggio et al. 2018; Ziemssen et al. 2018). As such, there remains a substantial unmet need for an optimized treatment and dosing regimen that

could alleviate the current treatment burden while maintaining improved vision outcomes in clinical practice (Ciulla et al. 2003; Ciulla et al. 2018).

The lack of compliance with treatment in patients with moderately severe or severe NPDR was found to be associated with disease progression to visual-threatening manifestations. The occurrence of DME and PDR was found to be relatively high in such patients, when they are not treated with anti-VEGF (Sloan et al. 2014; Obeid et al. 2018; Wubben and Johnson 2019).

Based on the totality of evidence from the Phase I, *II*, and III studies in PDS for nAMD, and taking into account extensive clinical experience with ranibizumab and its well established benefits in the treatment also of DR (see Section 1.2), it is anticipated that the continuous delivery of ranibizumab via the PDS implant in patients with DR will lead to superior efficacy when compared with observation with no treatment, which is currently a common practice given the treatment burden. In addition, delivering ranibizumab via the PDS instead of via monthly or frequent intravitreal injections could represent a less burdensome treatment option and therefore an important advantage for patients with DR, supporting adherence to a treatment regimen that may address the current unmet need in this population.

The PDS implant is designed as a surgically implantable, permanent ocular medical device. Use of the PDS involves surgical implantation (and explantation, if required), as well as refill-exchange. These procedures have their own inherent risks, in addition to the risks associated with ranibizumab as a drug. The procedural risks in using the PDS are associated with three independent aspects: initial implantation, periodic implant refill–exchange of drug, and long-term intraocular presence of the implant. For the anticipated risks associated with the PDS implant and/or its procedures, which include vitreous hemorrhage, conjunctival erosion, rhegmatogenous retinal detachment, endophthalmitis, device dislocation, septum dislodgement, conjunctival retraction, and conjunctival bleb (see Section 5.1.2). These risks are well understood and described in detail in Section 6 of the PDS Investigator's Brochure. Guidance on how to manage these risks, if they occur, is provided in Section 5.1.5 of this protocol.

An assessment was conducted to determine whether there is any impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment of this study, including, but not limited to, the patient population under study, study treatment(s), and/or treatment combination being evaluated. Based on that assessment, no impact is anticipated and the existing safety monitoring and management guidelines, and risk–mitigation measures provided in the study protocol are considered adequate.

2. OBJECTIVES AND ENDPOINTS

This study is a multicenter, randomized, visual assessor–masked study in patients with DR without center-involved DME (CI-DME) to evaluate the efficacy, safety, and pharmacokinetics of ranibizumab 100 mg/mL delivered via the PDS every 36 weeks (Q36W) relative to the comparator arm (see Section 3.1.1). Specific objectives and corresponding endpoints for the study are outlined below.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the superior efficacy of ranibizumab 100 mg/mL delivered via the PDS Q36W compared with observation on the basis of the following endpoint measured in the study eye:

- Proportion of patients with a ≥2-step improvement on the ETDRS-DRSS from baseline at Week 52

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of ranibizumab 100 mg/mL delivered via the PDS Q36W relative to the comparator arm on the basis of the following endpoints measured in the study eye:

- Rate of patients developing a vision-threatening complication (defined as PDR or anterior segment neovascularization [ASNV]) or CI-DME [defined as central subfield thickness [CST] ≥325 μm on spectral-domain optical coherence tomography [SD-OCT]) through Week 52
- Rate of patients developing PDR or ASNV through Week 52
- Rate of patients developing CI-DME through Week 52
- Rate of patients developing a ≥2-step worsening from baseline on the ETDRS-DRSS through Week 52
- Proportion of patients with a ≥3-step improvement from baseline on the ETDRS-DRSS at Week 52
- *Rate* of patients *developing* a ≥3-step worsening from baseline on the ETDRS-DRSS *through* Week 52
- Proportion of patients with a ≥2-step improvement from baseline on the ETDRS-DRSS over time
- Proportion of patients with a ≥3-step improvement from baseline on the ETDRS-DRSS over time
- Time to first development of either PDR, ASNV, or CI-DME
- Time to first development of PDR or ASNV
- Time to first development of CI-DME
- Time to first development of a ≥2-step worsening from baseline on the ETDRS-DRSS

- Time to first development of a ≥3-step worsening from baseline on the ETDRS-DRSS
- Change from baseline in BCVA as measured on the ETDRS chart over time
- Proportion of patients who lose <15, <10, and <5 letters in BCVA from baseline over time
- Proportion of patients with a BCVA score of 69 letters (20/40 approximate Snellen equivalent) or better over time
- Change from baseline in CST as measured on SD-OCT over time
- Change from baseline in total macular volume as measured on SD-OCT over time
- *Proportion of patients with absence of intraretinal fluid, subretinal fluid, or both (as measured in the central 1 mm subfield) over time*
- Proportion of patients who do not undergo supplemental treatment with intravitreal ranibizumab within each refill-exchange interval
- *Proportion of patients who report preferring PDS treatment to intravitreal ranibizumab treatment, as measured by the PPPQ at Week 52*

2.1.3 Exploratory Efficacy Objective

The exploratory efficacy objectives for this study are the following:

- To evaluate the efficacy of ranibizumab 100 mg/mL delivered via the PDS Q36W compared with observation on the basis of the following endpoints:
  - Change from baseline in total area of retinal non-perfusion and retinal ischemia over time
  - Time to first vitrectomy for complications of PDR
  - Time to first PRP
  - Proportion of patients that receive supplemental treatment after the PDS implant insertion and number of supplemental treatments patients receive
  - Proportion of patients in the comparator arm that receive an intravitreal ranibizumab 0.5 mg injection and the number of intravitreal treatments patients receive prior to Week 52
- To evaluate advanced analytics tools (e.g., artificial intelligence-based tools) to predict progression to visual-threatening presentations of DR

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety and tolerability of ranibizumab 100 mg/mL delivered via the PDS on the basis of the following endpoints:

- Incidence and severity of ocular adverse events
- Incidence and severity of non-ocular adverse events
- Incidence, severity, and duration of adverse events of special interest, including ocular adverse events of special interest

- Incidence, severity, and duration of ocular adverse events of special interest during the postoperative period (≤37 days after initial implant insertion) and follow-up period (>37 days after implant insertion surgery)

The device safety objectives for this study are to evaluate the device and *procedure-related* safety on the basis of the following endpoints:

- Incidence and severity of adverse device effects
- Incidence, causality, severity, and duration of anticipated serious adverse device effects

2.3 PHARMACOKINETIC OBJECTIVES

The pharmacokinetic (PK) objective for this study is to characterize the serum PK profile of ranibizumab 100 mg/mL delivered via the PDS after the initial and subsequent refill-exchange procedures in patients with DR on the basis of the following endpoints:

- Serum concentrations of ranibizumab observed over time
- Additional estimated PK parameter values, including area under the concentration–time curve, *maximum serum concentration,* minimum serum concentration observed, and half-life after PDS implant insertion

The exploratory PK objectives for this study are to evaluate potential relationships between drug exposure and the efficacy and safety of ranibizumab and to characterize ranibizumab aqueous humor concentration over time delivered via the PDS on the basis of the following endpoints:

- Relationship between serum concentrations or PK parameters for ranibizumab delivered via the PDS and efficacy endpoints
- Relationship between serum concentrations or PK parameters for ranibizumab delivered via the PDS and safety endpoints
- Measured aqueous humor concentrations of ranibizumab over time

2.4 IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to ranibizumab 100 mg/mL delivered via the PDS on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) prior to study treatment and incidence of ADAs after study treatment
- *Prevalence of neutralizing antibodies at baseline and incidence of neutralizing antibodies during the study*

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs *and neutralizing antibodies* on the basis of the following endpoint:

- Relationship between ADA status and *neutralizing antibodies and* efficacy, safety, or PK endpoints

2.5 *EXPLORATORY* BIOMARKER OBJECTIVES

The exploratory biomarker objectives for this study are to identify biomarkers that are predictive of response to ranibizumab, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can provide evidence of ranibizumab activity, or can increase the knowledge and understanding of disease biology, on the basis of the following endpoints:

- Correlation between concentration of free VEGF (VEGF not in complex with ranibizumab) in aqueous humor at baseline and over time with PK and/or efficacy endpoints
- Correlation between concentration of free VEGF in aqueous humor at baseline and over time with DR progression
- Relationship between genetic variants (such as polymorphisms within the VEGF-A genetic locus) with the disease characteristics and/or response to treatment with ranibizumab
- Relationship between baseline imaging features and response to treatment with ranibizumab or other efficacy endpoints over time
- Relationship between baseline imaging features and DR progression

2.6 PATIENT TREATMENT EXPERIENCE OBJECTIVES

The patient treatment experience objectives for this study are to evaluate patient treatment satisfaction. *These objectives will be evaluated by* the following endpoint:

- Mean overall treatment satisfaction as measured by the Retinopathy Treatment Satisfaction Questionnaire, status version (RetTSQs) total score at Week 52

2.7 DEVICE AND PROCEDURE EXPERIENCE OBJECTIVE

The device and procedure experience objective for this study is *to* characterize the safety (as detailed in Section 2.2) of the PDS devices and procedures *on the basis of the following endpoint:*

- *Reported incidence of device deficiencies*

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

Study GR41675 is a multicenter, randomized, visual assessor–masked study in patients with DR without CI-DME to evaluate the efficacy, safety, and pharmacokinetics of ranibizumab 100 mg/mL delivered via PDS Q36W relative to the comparator arm.

3.1.1 Overview of Study Design

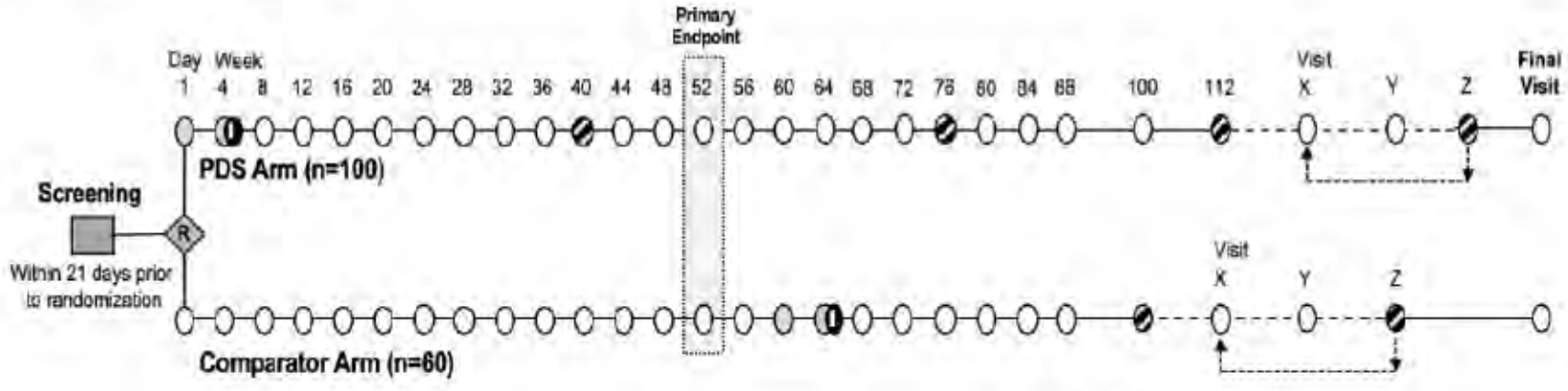
Approximately 160 patients with moderately severe or severe NPDR (DRSS level 47 or 53) without CI-DME will be enrolled at approximately 100 investigational sites. Patients who are naive to any treatment for DR in the study eye are eligible for screening.

During the screening period, the inclusion and exclusion criteria will be assessed and eligibility to participate in the study will be determined (see Section 4.1 for inclusion and exclusion criteria). Patients who are eligible to participate in the study will be randomized in a 5:3 ratio to one of two arms stratified by baseline ETDRS-DRSS level (47 vs. 53) and intraretinal or subretinal fluid status on SD-OCT (present vs. absent) as assessed at baseline by a central reading center (see Figure 1).

The two study arms are as follows (see Section 3.1.4 for additional details):

- **PDS Arm** (n = 100): Patients randomized to the PDS arm will receive two loading doses with intravitreal ranibizumab 0.5-mg injections before the PDS implant procedure. The first loading dose will be administered at the end of the Day 1 visit. The second loading dose will be administered at the Week 4 visit (±7 days). The PDS implant (pre-filled with ranibizumab 100 mg/mL) will be surgically inserted 1–14 days after the second loading dose and within the Week 4 visit window. Patients will undergo PDS implant refill-exchange procedures (ranibizumab 100 mg/mL) Q36W thereafter.
- **Comparator Arm** (n = 60): Patients randomized to the comparator arm will undergo study visits every 4 weeks (Q4W) for observation and comprehensive clinical monitoring for the first 60 weeks. After the observation period, patients will receive two loading doses with intravitreal ranibizumab 0.5 mg injections before PDS implant insertion surgery. The first loading dose will be administered at the end of the Week 60 visit. The second loading dose will be administered at the Week 64 visit (±7 days). The PDS implant (pre-filled with ranibizumab 100 mg/mL) will be surgically inserted 1–14 days after the second loading dose and within the Week 64 visit window. Patients will receive PDS implant refill-exchange procedures (ranibizumab 100 mg/mL) Q36W thereafter.

Figure 1 Study Schema



PDS = Port Delivery System with ranibizumab.

3.1.2 Screening

Informed consent must be administered to and signed by patients before any study-specific screening procedures are performed. Each consented patient must satisfy the eligibility criteria as applicable at screening (see Sections 4.1.1 and 4.1.2).

As part of the screening process, color fundus photography (CFP), fluorescein angiography (FA), and SD-OCT images will be obtained. A central reading center will evaluate fundus images as appropriate to provide an objective assessment of patient eligibility.

Patients who do not meet eligibility criteria (i.e., screen-failed patients) may be eligible to repeat screening up to two times, at the investigator's discretion.

At rescreening, a new screening number will be assigned to the patient through an interactive voice- or web-based response system (IxRS) and all screening assessments will be performed. Glycosylated hemoglobin (HbA_{1c}) measurements taken within 2 months prior to rescreening visit and reading-center-accepted FA images taken within 3 months prior to rescreening can be accepted and do not have to be repeated.

If HbA_{1c} is >12% at screening, it can be retested within the 21-day screening period, if deemed appropriate by the investigator. The most recent HbA_{1c} test results will be considered for eligibility. The patient may proceed to randomization visit if HbA_{1c} level is ≤12% provided that all other eligibility criteria are met *(see Section 4.1.1.1)*.

Patients who have been screened as outlined in Protocol GR40550 (*DME* trial; Pagoda) who do not meet eligibility criteria for Pagoda trial (GR40550) may submit their Pagoda acquired screening images, and laboratory biomarker, and other biological sample results to be used for screening *in Study* GR41675 (Pavilion) within 21 days of their initial collection with the exception of reading center–accepted FA images, which can be submitted if taken within 3 months of the GR41675 screening visit.

3.1.3 Randomization

The randomization day (Day 1) assessments will be completed according to the schedule of activities in Appendix 2 and Appendix 3. Once the patients are deemed eligible to participate in the study, with presence of moderately severe or severe NPDR (DRSS level 47 or 53) confirmed on CFP by the central reading center, and all inclusion and exclusion criteria are met per protocol, the patients will be randomized to either the PDS arm or the comparator arm within 21 days from the date when the first screening assessment is completed. Randomization will be stratified by ETDRS-DRSS level (47 vs. 53) and intraretinal or subretinal fluid status on SD-OCT (present vs. absent) as assessed at baseline by a central reading center.

Once patients are randomized, they will proceed with the schedule planned for each of the two study arms (see Section 3.1.1).

3.1.4 Comparator-Controlled Study Treatment Phase and PDS Extension Phase

3.1.4.1 PDS Arm

Patients randomized to the PDS arm will receive at least two loading doses with intravitreal ranibizumab 0.5 mg injections, administered at Day 1 and Week 4 visits. The first loading dose must be administered after the conclusion of the randomization visit assessments. At Week 4, patients must complete a pre-implant visit prior to the implant insertion surgery. Both visits must be completed within the Week 4 window and the PDS implant (pre-filled with ranibizumab 100 mg/mL) will be surgically inserted 1–14 days after the second loading dose (e.g., if the patient receives the second loading dose at Day 28 (Week 4), implant insertion surgery must occur no earlier than Day 29 and no later than Day 35).

If PDS implant insertion surgery cannot be completed within this required timeframe because of an extenuating circumstance, PDS implant insertion surgery may be postponed *following consultation* with *the* Medical Monitor (see Section 3.1.4.3).

Patients in the PDS arm will undergo refill-exchange procedures (ranibizumab 100 mg/mL) at Weeks 40, 76, 112, and Q36W thereafter (Visit Z refill-exchange visit) until the end of the study as outlined in Appendix 2.

After PDS implant insertion surgery, patients will undergo scheduled visits for safety assessments at the following times: the day immediately after the implant insertion surgery (post-implant insertion Visit 1); 7 (± 2) days after implant insertion surgery (post-implant insertion Visit 2); at the Week 8 visit (± 7 days); Q4W (± 7 days) thereafter until Week 88; and every 12 weeks (Q12W) (± 7 days) thereafter until the end of the study. Following delayed PDS implant insertion surgery, the timing of subsequent refill-exchange procedures will remain unchanged and should be administered as outlined in Appendix 2.

Patients in the PDS arm who meet specific clinical criteria (development of CI-DME or PDR/ASNV) per investigator assessment can receive supplemental treatment with intravitreal ranibizumab 0.5 mg injections per investigator's clinical judgment at any non–refill-exchange study visit during the study post implant (see Section 4.3.2.3).

3.1.4.2 Comparator Arm

Patients randomized to the comparator arm will undergo study visits Q4W for observation and comprehensive clinical monitoring. Beginning at Week 60, patients will receive two loading doses with intravitreal ranibizumab 0.5 mg injections, administered at the Week 60 and Week 64 visits. At Week 64, patients must complete a pre-implant visit prior to the implant insertion surgery. Both visits must be completed within the Week 64 window and the PDS implant (pre-filled with ranibizumab 100 mg/mL) surgically inserted 1–14 days after the Week 64 intravitreal injection.

Patients in the comparator arm will undergo a refill-exchange procedure with ranibizumab 100 mg/mL at Week 100 and Q36W thereafter (Visit Z refill-exchange visit) until the end of the study as outlined in Appendix 3.

If PDS implant insertion surgery cannot be completed within this required timeframe because of an extenuating circumstance, the PDS implant insertion may be postponed *following consultation* with *the* Medical Monitor (see Section 3.1.4.3).

After PDS implant insertion surgery, patients will undergo scheduled study visits for safety assessments at the following times: the day immediately after the implant insertion procedure (post-implant insertion Visit 1); 7 (±2) days after implant insertion (post-implant insertion Visit 2); at the visits at Weeks 68, 72, 76, 80, 84, and 88 (± 7 days); and Q12W (± 7 days) thereafter until the end of the study. Following delayed PDS implant insertion surgery, the timing of subsequent refill-exchange procedures will remain unchanged and should be administered as outlined in Appendix 3.

After randomization (Day 1) and until the Week 56 visit (i.e., the comparator-controlled study treatment phase), patients randomized to the comparator arm who meet specific clinical criteria (development of CI-DME or PDR/ASNV; Section 4.3.2.3) per investigator assessment can be treated with supplemental intravitreal ranibizumab 0.5 mg injections. The protocol criteria must be met for the first supplemental intravitreal ranibizumab treatment; subsequent supplemental treatments in the comparator arm can be done per investigator discretion (Section 4.3.2.3).

After the Week 64 visit (i.e., the PDS extension phase), comparator arm patients with the PDS implant who meet specific clinical criteria (development of CI-DME or PDR/ASNV) per investigator assessment can receive supplemental treatment with intravitreal ranibizumab 0.5 mg injections per investigator's discretion at any non-refill-exchange study visit during the study (see Section 4.3.2.3).

3.1.4.3 General Instructions for Both Study Arms

Patients should attempt to make all scheduled study visits; however, if extenuating circumstances preclude a scheduled study visit, patients should return for the next scheduled study visit. If the next scheduled study visit is more than 4 weeks from the missed visit (e.g., the patient misses a study visit at Week 88 or later and the next scheduled visit will take place in 12 weeks), the patient should return within 4 weeks for a separate study visit. Following completion of the study visit, patients will continue with originally scheduled Q12W visits per protocol (see Appendix 2 or Appendix 3).

Beginning at Week 88, all patients will return Q12W for study visits and study-specific assessments. Optional study visits between each mandatory Q12W visit may be added per investigator discretion. Study visits will occur according to the schedules of activities in Appendix 2 and Appendix 3 and will continue until the patient completes participation in the study.

Patients will be contacted by site personnel 3 (±1) days after each intravitreal ranibizumab injection or refill-exchange procedure to elicit reports of eye pain, decrease in vision, unusual redness, or any other new ocular symptoms in the study eye. All patients receiving the PDS implant will also be asked to verify whether they have taken the prescribed, self-administered, post-treatment topical medications (see Appendix 17).

In the event a patient's fellow eye (non–study eye) requires treatment for DR starting from the screening visit, the fellow eye may be treated per standard of care in accordance with local regulations. If the investigator chooses to treat the fellow eye with ranibizumab, the Sponsor will provide *intravitreal* ranibizumab 0.3 mg as per local label and regulations starting from the screening visit. Study eye treatment and fellow eye treatment may be administered at the same study visit. However, all study eye assessments and study eye treatment, should be completed per protocol first, followed by treatment in the fellow eye.

All patients will complete a final study visit after completion of study treatment (see Section 3.2). Patients who prematurely discontinue from study treatment will be encouraged to continue participating in the study and attend as many visits as possible, with an emphasis on the Week 52 visit (see Section 4.6.1). Patients who cannot comply with protocol requirements, including the PDS implant procedure, may be discontinued from the study (see Section 4.6.2). Patients who are prematurely discontinued from the study will complete an early termination visit (see Section 4.6.2).

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

Study investigators will be qualified ophthalmologists, trained in the management of retinal diseases and ocular surgery. *Study investigators performing PDS procedures* will be trained by the Sponsor to perform study-specific PDS implant insertion surgery, refill-exchange procedure, and explantation procedures. The surgical procedures involved in the use of the investigational devices are also detailed in the PDS IFU document. If an investigator is not able to follow the current *instructions for use* (IFU), the Sponsor may decide to intervene (e.g., pause in recruitment, re-training, or replacement of *the* investigator).

It is strongly preferred that each site has one investigator who evaluates and treats all patients, with backup investigators selected. The site may opt to have more than one investigator, but to maintain consistency in the evaluation and treatment of patients, it is strongly suggested that the same physician conduct the evaluation and treatment of each individual patient throughout the trial.

Postponement of PDS Implant Insertion

If PDS implant insertion surgery cannot be completed within the required timeframe (1–14 days after intravitreal ranibizumab 0.5 mg injection and within the study visit

window) because of an extenuating circumstance, the PDS implant insertion may be postponed once for approximately 4 weeks *following consultation* with *the* Medical Monitor. If *the decision is to postpone insertion of the implant, then* the patient will receive an additional intravitreal ranibizumab 0.5 mg injection at the next scheduled Q4W study visit and will then have the PDS implant (pre-filled with ranibizumab 100 mg/mL) surgically inserted 1–14 days after the intravitreal injection and within the same visit window. For example, if a patient in the PDS arm receives the additional loading dose at Day 56 (Week 8), implant insertion surgery must occur no earlier than Day 57 and no later than Day 63, or if a patient in comparator arm receives the additional loading dose at Day 476 (Week 68), implant insertion surgery must occur no earlier than Day 477 and no later than Day 483. Patients who have had their surgeries delayed by 1 month will follow the modified assessments as outlined in Appendix 2 and Appendix 3.

If PDS implant insertion surgery cannot be completed by Week 8 (PDS arm) or Week 68 (Comparator arm), the patient will be withdrawn from the study and will be required to return for an early termination evaluation visit 30 (+ 7) days following the last intravitreal ranibizumab injection for monitoring of all adverse events (serious and non-serious) and early termination assessments (see Appendix 2 and Appendix 3).

In cases of septum dislodgement, after consultation with the Medical Monitor, a patient may receive a new implant following explantation of the original implant. Patients must undergo new implant insertion at the time of explantation using the original incision site to place the new implant. If clinically indicated, upon consultation with the Medical Monitor, the patient can receive Sponsor-supplied intravitreal ranibizumab 0.5 mg in the study eye for the treatment of DR prior to explantation and new implant insertion. If a patient cannot undergo re-implantation or if an anti-VEGF agent other than ranibizumab is administered in the study eye, the patient must be discontinued from study treatment (as no additional refill-exchange procedures can be performed; see Sections 4.4.2 and 4.6.1).

3.1.5 Internal Safety Monitoring

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

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

3.1.6 Independent Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will monitor safety on an ongoing basis. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines the committee's roles and responsibilities. The iDMC will meet approximately

every 6 months (frequency adjustable as required) to evaluate unmasked safety data (including significant decreases in BCVA), which will be prepared for the committee by an independent Data Coordinating Center (iDCC). The iDMC will provide recommendations to the Sponsor's Data Review Board (DRB) Chair as described in the iDMC Charter. On behalf of the Sponsor, the DRB Chair will accept or reject the recommendations.

Full details regarding the roles and responsibilities of the iDMC will be provided in the charter.

A nominal type I error penalty of 0.0001 (two-sided) will be taken for each time the iDMC reviews unmasked data prior to the formal analysis of the primary efficacy endpoint. At the time of the primary *efficacy endpoint* analysis, it is estimated that four interim data reviews will have been conducted by the iDMC; therefore, efficacy analyses will be performed at a significance level of 0.0496. The actual adjustment will depend on the actual number of iDMC meetings.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the study is defined as the date when the last patient in the study completes their final study visit.

The duration of this study will depend on health authority approval of the PDS for this indication, as well as Sponsor decision. In the event the PDS receives health authority approval for this indication prior to 112 weeks after the last patient is randomized in this study, the Sponsor may request completion of the final visit prior to this date.

In addition, the Sponsor may decide to terminate the study at any time.

3.3 RATIONALE FOR STUDY DESIGN

The investigational PDS is being studied as an alternate means of delivering ranibizumab in patients with DR. Providing ranibizumab treatment through an implant designed to provide continuous drug delivery may reduce the number of required office visits and the frequency of drug administration necessary in clinical practice, while achieving efficacy similar to that observed in previous pivotal intravitreal anti-VEGF trials. In addition, improved compliance that may result from such a regimen may lead to better long-term vision outcomes for patients.

3.3.1 Rationale for Ranibizumab Dose and Schedule

The dose of ranibizumab 100 mg/mL administered to patients via the PDS implant and the 36-week refill-exchange interval were selected on the basis of the following reasons:

- Observed efficacy and safety data from the Ladder trial, which evaluated a range of ranibizumab formulations (PDS 10 mg/mL, PDS 40 mg/mL, and PDS 100 mg/mL) and a refill-exchange dosing regimen based on pre-specified criteria in patients with nAMD

- Ocular VEGF levels in patient populations with DR (Funatsu 2005)
- Modeling and simulation of VEGF suppression with the PDS PK profile and estimates for VEGF production in the patient population with DR
- Relative ocular and systemic exposure between intravitreal ranibizumab injections (0.3 mg Q4W or 0.5 mg Q4W) and PDS (100 mg/mL Q36W), as estimated in patients with DR

The observed data from the Ladder trial and PK-efficacy modeling and simulation supported the dose selection of PDS 100 mg/mL Q24W for the Phase III Archway trial in patients with nAMD, which achieved efficacy comparable to intravitreal ranibizumab 0.5 mg Q4W. However, a longer refill-exchange interval of Q36W has been selected for this NPDR population since vitreal and aqueous VEGF levels have been shown to increase with increased DRSS level (Funatsu 2005), suggesting that this patient population may have a lower VEGF burden and be able to maintain VEGF suppression with lower anti-VEGF concentrations. Using a PK/pharmacodynamics (PD) model of VEGF suppression developed with data from intravitreal administration of ranibizumab and assuming VEGF production in this patient population with DR is 60% or less of VEGF production in patients with nAMD, the vitreous VEGF levels for a typical patient with DR with PDS 100 mg/mL at 36 weeks after refill-exchange procedure would be similar to a typical patient with nAMD with PDS 100 mg/mL at 24 weeks after refill-exchange procedure.

Additionally, no differences in pharmacokinetics have been seen across different indications (nAMD, DME, DR, or retinal vein occlusion) following intravitreal ranibizumab injections.

Total local (i.e., vitreal) and systemic drug exposures (area under the concentration–time curve) with the PDS 100-mg/mL Q36W are estimated to be below the drug exposures from monthly intravitreal ranibizumab 0.3 mg or 0.5 mg injections, which are exposure levels that have been shown to be well-tolerated.

Based on the implant fill volume of 20 µL, the maximum amount of ranibizumab that can be initially filled and subsequently refilled is approximately 2 mg of ranibizumab for the 100-mg/mL formulation.

Taken together, the PDS 100 mg/mL is anticipated to deliver pharmacologically efficacious concentrations of ranibizumab in the majority of patients in the study population over the entire dosing interval of 36 weeks, with well-tolerated drug exposures.

3.3.2 Rationale for Patient Population

Data from a Phase III, double-masked, randomized study of intravitreal aflibercept injection in patients with moderately severe to severe NPDR (Panorama trial, ClinicalTrials.gov identifier: NCT02718326, EudraCT number: 2016-002639-14, Boyer et

al. 2019; Brown 2018), showed that 40.6% of patients in the sham arm developed CI-DME or PDR/ASNV through Week 52 and required treatment with intravitreal anti-VEGF injection. Ranibizumab has been shown to be effective in improving and maintaining DR severity and is correlated with greater magnitudes of functional and anatomic improvement (Ip et al. 2017). Among DR severity subsets, patients with moderately severe or severe NPDR (DRSS level 47 or 53) showed greatest benefits in preventing DR progression and vision loss due to visual-threatening complications following ranibizumab treatment (Wykoff et al. 2018); therefore, this patient population was selected to evaluate the PDS with ranibizumab 100 mg/mL Q36W. Patients must also meet all of the eligibility criteria for this protocol (for the inclusion and exclusion criteria, see Sections 4.1.1 and 4.1.2, respectively). Only patients who are naive to any treatment for DR in the study eye are eligible for screening.

The goal of exposing patients with DR to the investigational PDS is to demonstrate a treatment approach that offers superior outcomes in comparison to observation without treatment, while offering the potential for reduced monitoring, more sustained disease control, and better long-term anatomic and visual outcomes than currently observed in clinical practice, since lack of compliance with the monthly treatment regimen can lead to suboptimal efficacy (Holekamp et al. 2018; Wubben et al. 2019).

3.3.3 Rationale for Comparator Group

This study is an interventional study, aiming to evaluate the superiority in efficacy of the PDS with ranibizumab 100-mg/mL formulation compared with observation. While anti-VEGF therapy is clinically indicated for DR, and the label-approved treatment regimens support anti-VEGF use as frequent as Q4W (Lucentis U.S. Package Insert), current practice patterns for NPDR eyes show a range in treatment approaches, from observation only to less than monthly dosing (AAO 2017). The comparator arm in this study reflects current real-world practice patterns.

3.3.4 Rationale for Pharmacokinetic Sample Collection Schedule

The objectives of the serum PK sampling are to characterize the serum pharmacokinetics of ranibizumab delivered via the PDS, to assess the potential impact of immunogenicity on pharmacokinetics, and to explore potential relationships between pharmacokinetics and efficacy, safety, or biomarkers.

In this study, PK serum samples will be collected at all sites from patients in the PDS arm and from patients in the comparator arm to characterize release from the PDS implant and to align with ADA sample collection timepoints. No serum PK samples will be collected *from patients* in the comparator arm until Week 60 when they will first start receiving scheduled ranibizumab. The sampling timepoints through Week 40 in the PDS arm are expected to be sufficient to estimate the half-life for ranibizumab delivery from the PDS implant in patients with DR; sampling timepoints beyond Week 40 will be assessed to ensure consistent drug delivery over time.

See Appendix 2 and Appendix 3 for sample collection timepoints.

3.3.5 Rationale for Immunogenicity Sample Collection

The objective of serum sampling for ADA testing is to characterize the immunogenicity of ranibizumab delivered via the PDS. The immunogenicity of ranibizumab following intravitreal administration has been well characterized, and the incidence of ADAs in the context of the delivery system in the Phase II Ladder trial was not considered to have been markedly different. The sampling timepoints for ADA assessment will ensure that the anti-ranibizumab immunogenicity profile of patients in the study is properly monitored in the study.

Serum ADA samples will be collected from all patients in the PDS arm and comparator arm at multiple timepoints (see Appendix 2 and Appendix 3).

3.3.6 Rationale for Biomarker Assessments

Previous studies in various indications have demonstrated a broad range of treatment needs across patients (Elman et al. 2010; International Council of Ophthalmology 2017; Payne et al. 2017; Shah and Stone 2017); thus, some patients in the PDS arm may require additional treatment(s) with ranibizumab outside of the fixed 36-week dosing interval. To better understand the cause of their increased treatment needs, aqueous humor and plasma samples from patients who require supplemental intravitreal ranibizumab treatment will be collected (just prior to the supplemental treatment and at the next subsequent visit) and analyzed for drug and/or free VEGF concentrations and correlated with retreatment need. In addition, aqueous humor and plasma samples will be collected from patients who terminate study treatment early or who undergo explantation. Information obtained from these analyses will be used in an effort to better understand variability in treatment need and to identify patients best suited for continuous delivery of ranibizumab.

3.3.7 Rationale for Device and Procedure Assessments

The *cumulative body of evidence from the* clinical Phase II Study GX28228 (Ladder) *and Phase III Study GR40548 (Archway) have* demonstrated that the PDS devices performed as intended, have a favorable benefit–risk profile *for the treatment of patients with nAMD,* and *are* supportive of the registration of the PDS devices globally. *The ongoing open-label extension Study GR40549 (Portal) continues to evaluate the long-term safety and efficacy.*

In addition, the performance *of the PDS implant* was assessed indirectly through observation of serum and aqueous humor or vitreous concentrations of ranibizumab and by assessment of explanted implants. Device clinical results, paired with bench performance testing of removed implants, demonstrated no evidence of device clogging in any of the 179 implants ([90% CI: 0 to 2.0], Report No. *1105202*).

Based on these results, PDS drug release, and therefore implant performance, has already been demonstrated. Therefore, in order to meet the safety reporting requirements of International Organization for Standardization (ISO®) 14155:2020 and the E.U. Medical Device Regulation (E.U. MDR 2017/745), this study, GR41675, will focus on device/procedure safety data collection.

All adverse events will be categorized by their relationship to the study drug, the PDS devices, and/or *PDS* associated procedures *(implant insertion, refill-exchange, or explantation),* according to the parameters defined in Section 5.1.5.8. Adverse events causally related to device or procedure are known as adverse device effects (defined in Section 5.2.2.1). Within the adverse device effect category, anticipated serious adverse device effects have been identified in Section 5.2.2.3, and unanticipated serious adverse device effects are described in Section 5.2.2.4.

3.4 EXPLORATORY SUBSTUDIES

At selected sites, the Sponsor may propose exploratory substudies associated with this protocol (Study GR41675). If so, substudies will be developed in accordance with local requirements. Each substudy will be documented in a separate substudy protocol and will utilize separate Informed Consent Form(s).

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 160 patients with a diagnosis of moderately severe or severe NPDR (ETDRS-DRSS level 47 or 53) secondary to diabetes mellitus (Type 1 or 2) without CI-DME will be evaluated for participation in the study based on the eligibility criteria described below.

Only patients who are naive to any treatment for DR in the study eye are eligible for screening.

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

4.1.1 Inclusion Criteria

4.1.1.1 General Inclusion Criteria

Patients must meet the following general inclusion criteria for study entry:

- Ability and willingness to provide signed Informed Consent Form
- Age ≥18 years at time of signing Informed Consent Form
- Ability and willingness to comply with the study protocol and to undertake all scheduled visits and assessments, in the investigator's judgment
- Documented diagnosis of diabetes mellitus (Type 1 or Type 2), as defined by the American Diabetes Association or per WHO criteria and
  - Current regular use of insulin for the treatment of diabetes

and/or

- Current regular use of anti-hyperglycemic agents for the treatment of diabetes

- HbA_{1c} level of ≤ 12% within 2 months prior to screening or at screening

  HbA_{1c} can be retested within the 21-day screening period with the most recent results considered for eligibility (see Section 3.1.2 for details).

- Willingness to adhere to recommendations/measures provided by their endocrinologist or primary care physician to aim for the best possible metabolic control during participation in the study
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for at least *3 months* after the final intravitreal injection of ranibizumab or 1 year after the final refill-exchange of ranibizumab.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

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

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

4.1.1.2 Ocular Inclusion Criteria for Study Eye

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

- Moderately severe or severe NPDR (ETDRS-DRSS level 47 or 53) as assessed by the investigator and confirmed by the central reading center
- BCVA of ≥69 letters (20/40 approximate Snellen equivalent or better), using the ETDRS protocol at the initial testing distance of 4 meters (see Appendix 7 and the BCVA specifications manual for additional details)

- Sufficiently clear ocular media and adequate pupillary dilatation to allow for analysis and grading by the central reading center

4.1.2 Exclusion Criteria

4.1.2.1 General Exclusion Criteria

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

- Currently untreated diabetes mellitus or previously untreated patients who initiated anti-diabetic medication or insulin within 3 months prior to randomization
- History of allergy or hypersensitivity to fluorescein or to any study-assessment or study treatment–related mandatory ingredients (e.g., disinfectants, anesthetics, etc.) that is not amenable to treatment
- Active cancer within the past 12 months, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or prostate cancer with a Gleason score of ≤6 and a stable prostate-specific antigen for >12 months
- Current systemic treatment for a confirmed active systemic infection
- Renal failure requiring renal transplant, hemodialysis, or peritoneal dialysis, or anticipated to require hemodialysis or peritoneal dialysis at any time during the study
- History of other disease, other non-diabetic metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a condition that contraindicates the use of ranibizumab or surgical placement of the PDS implant; that might affect interpretation of the results of the study; or that renders the patient at high risk for treatment complications in the opinion of the investigator or Sponsor
- Uncontrolled blood pressure (defined as systolic >180 mmHg and/or diastolic >110 mmHg while a patient is at rest) at screening

  If a patient's initial measurement exceeds these values, a second reading may be taken 30 or more minutes later. If the patient's blood pressure must be controlled by antihypertensive medication, the patient may become eligible if medication is taken continuously for at least 30 days.
- Cerebrovascular accident or myocardial infarction within 6 months prior to randomization
- Atrial fibrillation diagnosis or worsening within 6 months prior to randomization
- Use of any systemic anti-VEGF agents
- Participation in an investigational trial that involves treatment with any drug or device (with the exception of vitamins and minerals) within 6 months prior to randomization
- Administration of systemic pro-angiogenic treatments, such as VEGF-based therapies for peripheral or coronary ischemia (e.g., limb ischemia or myocardial infarction) within 6 months or 5 elimination half-lives

- Use of antimitotic or antimetabolite therapy within 30 days or 5 elimination half-lives
- Requirement for continuous use of any medications and treatments indicated in Section 4.4.2, Prohibited Therapy
- Pregnant or breastfeeding, or intending to become pregnant during the study treatment period and for at least *3 months* after the final intravitreal injection of ranibizumab or 1 year after the final refill-exchange of ranibizumab

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

4.1.2.2 Ocular Exclusion Criteria for Study Eye

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

- ETDRS-DRSS level other than level 47 or 53
- Presence of CI-DME (defined as CST ≥325 μm)
- Tractional retinal detachment or pre-retinal fibrosis
- Clinically significant abnormalities of the vitreous-retinal interface involving the macular area or disrupting the macular architecture, such as vitreous-retinal traction or epiretinal membrane (assessed by the investigator and confirmed by the central reading center)
- History of macular hole (Stage 3 or 4)
- Active rubeosis
- Active intraocular inflammation (grade trace or above)
- Any intravitreal anti-VEGF treatment at any time prior to randomization
- Any use of medicated intraocular implants, including Ozurdex® or Iluvien® implants, at any time prior to randomization
- Any intravitreal corticosteroid treatment at any time prior to randomization
- Any periocular (e.g., subtenon) corticosteroid treatment at any time prior to randomization
- Any PRP at any time prior to randomization
- Any macular laser photocoagulation (such as micropulse and focal or grid laser) at any time prior to randomization
- Retinal tears or peripheral retinal breaks, diagnosed within 3 months prior to randomization
- History of rhegmatogenous retinal detachment
- History of glaucoma-filtering surgery, tube shunts, or microinvasive glaucoma surgery

- Uncontrolled ocular hypertension or glaucoma (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 the investigator determines may require a glaucoma-filtering surgery during a patient's participation in the study
- Intraocular surgery (including cataract surgery) within 3 months prior to randomization
- History of corneal transplant
- History of pars plana vitrectomy
- Previous intraocular device implant insertion, unless it is a posterior chamber intraocular lens
- Aphakia or absence of the posterior capsule

  Previous violation of the posterior capsule is also an exclusion criterion unless it occurred as a result of yttrium-aluminum garnet laser posterior capsulotomy in association with prior, posterior chamber intraocular lens implant insertion.
- Spherical equivalent of the refractive error demonstrating more than 8 diopters of myopia

  For patients who have undergone prior refractive or cataract surgery in the study eye, preoperative refractive error that exceeds 8 diopters of myopia is an exclusion criterion.
- Diagnosis of concurrent or previous retinal diseases other than DR that can lead to macular edema
- Any concurrent ocular condition (e.g., cataract, epiretinal membrane) that would require surgical intervention during the study to prevent or treat visual loss that might result from that condition
- Any concurrent ocular condition (e.g., amblyopia, strabismus) that may affect interpretation of study results
- History of other ocular diseases that gives reasonable suspicion of a disease or condition that contraindicates the use of ranibizumab, that might affect interpretation of study results, or that renders the patient at high risk for treatment complications

4.1.2.3 Ocular Exclusion Criteria for Either Eye

Patients who meet any of the following exclusion criteria for either eye will be excluded from study entry:

- Suspected or active ocular or periocular infection (e.g., infectious conjunctivitis or endophthalmitis)
- Any history of uveitis (e.g., idiopathic, drug-associated or autoimmune-associated uveitis)

4.2 METHOD OF TREATMENT ASSIGNMENT AND MASKING

Patients will be randomly allocated to one of the two study arms in a 5:3 ratio so that approximately 100 patients (PDS arm) will receive the PDS implant with ranibizumab

100 mg/mL and Q36W refill-exchange procedures, and approximately 60 patients will be assigned to the comparator arm. Randomization will be performed through the IxRS. After randomization and at each study treatment visit, the IxRS will assign the appropriate study treatment kit to be used.

Randomization will be stratified by baseline ETDRS-DRSS level (47 vs. 53) and intraretinal or subretinal fluid status on SD-OCT (present vs. absent) as assessed at baseline by a central reading center. A stratified permuted-block randomization scheme will be used to obtain approximately a 5:3 ratio between the treatment groups overall and within each of the randomization strata. For analyses, the stratification factors as recorded in IxRS will be used.

Patients and study site personnel (except the BCVA examiner) will not be masked with regard to patient assignment to the PDS arm or the comparator arm because of the difficulties of maintaining masking following the surgical procedure. The Sponsor will require that the following steps be implemented as a best attempt to mask visual acuity (VA) examiners in order to minimize bias in VA assessments.

- The VA examiner will only conduct refraction and VA assessments and will be masked as best as possible to patient study eye assignment, study visit type, and patient treatment assignment.
- The VA examiner will have no access to a patient's BCVA scores from previous visits and will be aware only of the patient's refraction data from previous visits.
- The VA examiner may provide no other direct or indirect patient care.
- Patients and unmasked site personnel will be asked not to discuss the study eye assignment, study visit type, and patient treatment assignment with the VA examiner.
- Ocular images obtained from patients will be forwarded to an independent, masked central reading center for analysis (including assessment of DRSS level and OCT features) and/or storage.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

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

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Port Delivery System

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

The implant, insertion tool, initial fill needle, refill needle, and explant tool should be maintained at a room temperature *between 15°C and* 25°C (*59°F and* 77°F). The storage location at the clinical site must have restricted access and be available only to study personnel. The implant and insertion tool are supplied sterilized by exposure to ethylene oxide. The initial fill needle, refill needle, and explant tool are sterilized by electron-beam processing. The PDS devices are for single use only. Do not reuse the PDS components.

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

The packages should be opened only immediately prior to use.

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

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

4.3.1.2 Formulation of Ranibizumab Used in Implant (Initial Fill and Refill-Exchange)

Ranibizumab at 100 mg/mL will be supplied by the Sponsor for the initial fill and refill exchange procedures of the implant. Contents should not be frozen or shaken and should be protected from direct light. Ranibizumab must be refrigerated at 2°C–8°C (36°F–46°F) upon receipt until used. Sites must monitor and record refrigerator temperature at all times (24 hours per day, 7 days per week). **Store in original carton before and after use, unless site procedures differ.** All ranibizumab units will be labeled as required by the relevant regulatory agencies.

For further details, see the pharmacy manual.

4.3.1.3 Formulation of Ranibizumab for Intravitreal Injection

Ranibizumab for intravitreal injection will be supplied by the Sponsor and is formulated as a sterile, colorless to pale yellow solution. Ranibizumab contents should not be frozen or shaken and should be protected from direct light. Ranibizumab contents must be refrigerated at 2°C–8°C (36°F–46°F) upon receipt until used.

For further details, see pharmacy manual.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.1.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along

with any associated adverse events, should be reported as described in Section 5.3.6.11.

Guidelines for treatment interruption or discontinuation are provided in Section 4.6.1, Section 5.1.5.2, and Table 1.

4.3.2.1 Port Delivery System with Ranibizumab

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

Patients will have the PDS implant (filled prior to implant insertion with approximately 20 µL of the ranibizumab 100 mg/mL formulation) surgically inserted in the study eye at the Week 4 implant insertion visit (for the PDS arm) or at the Week 64 implant insertion visit (for the comparator arm). Subsequent refill-exchanges will be administered Q36W according to the study treatment schedule relative to the Week 4 visit (PDS arm) or Week 64 visit (comparator arm) as outlined in Appendix 2 and Appendix 3 until patients complete the study (see Section 3.2).

At each refill-exchange, a volume of approximately ranibizumab 100 µL will be injected in situ into the PDS implant through the conjunctiva and implant septum to exchange the remaining contents of the PDS implant with fresh ranibizumab 100 mg/mL. The volume of fresh ranibizumab (100 mg/mL) remaining in the implant after the refill-exchange procedure will be approximately 20 µL.

Missed implant refill-exchange *procedures* should be made up no later than the next scheduled study visit. If at the next scheduled study visit the refill-exchange cannot be performed, the investigator must contact the Sponsor for *a consultation* prior to performing future refill-exchange procedures. A missed refill-exchange at Week 112 or later (PDS arm) or Week 100 or later (comparator arm) should be made up no later than 4 weeks after the missed visit. After Week 112 (PDS arm) and Week 100 (comparator arm), subsequent visits are quarterly, so an additional visit is needed to administer the delayed refill-exchange procedure. If the refill-exchange cannot be performed within 4 weeks, the investigator must contact the Sponsor for further discussion prior to performing future refill-exchange procedures. Following refill-exchange, patients will continue with originally scheduled PDS Q36W refill-exchange procedures per protocol (see Appendix 2 or Appendix 3).

In cases of septum dislodgement, upon consultation with the Medical Monitor, a patient may receive a new implant following explantation of the original implant. Patients must undergo new implant insertion at the time of explantation using the original incision site to place the new implant. The new implant must be surgically inserted in the study eye at the re-implant visit (see Appendix 4). If the last study visit was completed more than 4 weeks (28 days) prior to the explantation/re-implantation scheduled date, an additional visit (as an unscheduled visit, Appendix 5) must be

performed. After re-implantation, patients will complete post–re-implantation study visits (see Appendix 4) and continue with the originally scheduled Q36W refill-exchange procedures per protocol (see Appendix 2 and Appendix 3, Section 3.1.4.1).

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

4.3.2.2 Intravitreal Ranibizumab 0.5 mg Injection

Intravitreal ranibizumab 0.5 mg injection will be used in the study eye as loading doses prior to PDS implant insertion on Day 1 and Week 4 for the PDS arm and on Weeks 60 and 64 for the comparator arm. The same dose will be administered in the study eye as supplemental intravitreal ranibizumab treatment for patients with the PDS in both arms that meet the criteria for supplemental treatment after PDS implantation, as treatment for patients randomized to the comparator arm before PDS implantation, *and as intravitreal ranibizumab treatment for patients awaiting the insertion of a new implant* (see Section 4.3.2.3).

4.3.2.3 Supplemental Intravitreal Ranibizumab 0.5 mg for Patients in Both Arms

Patients in the comparator arm will be eligible to receive supplemental intravitreal ranibizumab 0.5-mg injection at each scheduled Q4W visit before Week 60, and patients with the PDS implant (either arm) will be eligible for supplemental intravitreal ranibizumab 0.5 mg at any study visit, except at refill-exchange visits, if any of the following criteria are met in the study eye:

- Presence of CI-DME defined as CST ≥325 µm on SD-OCT as assessed by investigator

  or

- Development of PDR or ASNV, as assessed by investigator

Supplemental treatment for patients that meet the criteria above is not mandatory. Even if a patient meets the supplemental treatment criteria above, treatment may be withheld per clinical judgment at the investigator's discretion.

If a patient *in the comparator arm* meets the supplemental treatment criteria within the first 3 months after implant insertion *(i.e., if PDS implantation occurred at Week 64, and supplemental treament criteria are met during study visit Weeks 68 through 76),* the investigator must contact the Medical Monitor prior to administering supplemental intravitreal ranibizumab 0.5 mg treatment.

If a patient meets the supplemental treatment criteria and the investigator decides to administer supplemental intravitreal ranibizumab 0.5 mg, the assessments specified in Appendix 6 must be performed in addition to the assessments listed in Appendix 2 (patients in the PDS arm) or Appendix 3 (patients in the comparator arm after Week 64 once they have received the PDS implant).

At each visit at which supplemental intravitreal ranibizumab 0.5 mg is administered, the presence/absence of DME (as assessed by the investigator) and the presence/absence of PDR or ASNV (as assessed by the investigator) in the study eye will be entered into the IxRS.

If supplemental treatment is deemed necessary, the treatment must be administered at the end of the visit. If treatment cannot be administered at the end of the visit, patients will be asked to return within 7 days to receive supplemental treatment *(see* Appendix 6*)*. Following supplemental treatment, patients will continue with originally scheduled PDS Q36W refill-exchange procedures per protocol (see Appendix 2 or Appendix 3).

If, in the investigator's judgment, patients with progressive worsening of visual acuity, worsening of DR severity, or development of macular thickening due to CI-DME require additional treatment for DR in the study eye outside of protocol, the investigator must contact the Sponsor prior to administering such treatment.

If, in the investigator's clinical judgment, a patient requires PRP for DR progression in the study eye after the screening visit during participation in the study, the investigator must discuss the clinical indication with the Medical Monitor; in very specific cases, this therapy may be permitted.

4.3.3 *Investigational Device Handling and Accountability*

All investigational devices (PDS implant, insertion tool assembly, initial fill needle, refill needle, and explant tool) required for use in this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of device delivery to the site, device inventory at the site, device provision and use for each patient, destruction or return of unused devices (as applicable), thus enabling reconciliation of all devices received, and for ensuring that patients are provided with devices specified by the protocol.

The study site should follow all instructions included with each shipment of devices. The study site will acknowledge receipt of devices supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged or lost shipments will be replaced. All devices must be stored in a secure, environmentally controlled, and monitored (manual or automated) area, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive the investigational implant, and only authorized staff may supply the PDS devices. Unused devices will be returned to the Sponsor with the appropriate documentation, as per agreement. Accurate records of all devices received at, dispensed from, and returned to the study site should be recorded on the accountability log.

Refer to the pharmacy manual for information on investigational device handling, including preparation, storage, and accountability.

4.3.4 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (PDS with ranibizumab 100 mg/mL and ranibizumab 0.5 mg) will be provided by the Sponsor where required by local health authority regulations. The study site *(i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of investigational medicinal product (IMP) delivery to the site, IMP inventory at the site, IMP use by each patient, and destruction or return of unused IMP, thus enabling reconcilization of all IMP received, and for ensuring that patients are provided with doses specified by the protocol. The study site should follow all instructions included with each shipment of IMPs and* will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced, if IMP is needed.

The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by the time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff. Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs. Prior to site closure, IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation, except for all unused PDS components, which should be returned to the Sponsor. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form. Any unused or explanted PDS components should be returned to the Sponsor.

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

Refer to the pharmacy manual for information on the IMP handling, including preparations, storage, and accountability.

4.3.5 Continued Access to Port Delivery System with Ranibizumab and Intravitreal Ranibizumab

Currently, the Sponsor does not have any plans to provide Roche IMP (refill-exchanges or intravitreal ranibizumab injections) or any other study treatments to patients who have completed the study (i.e., completes final visit assessments as specified in Appendix 2 or Appendix 3). The Sponsor may evaluate whether to continue providing refill-exchanges or intravitreal ranibizumab injections in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

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

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment (Day 1) *in the PDS arm or from 7 days prior to randomization in the comparator arm* to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

At the time of publication of this protocol, there is no evidence to suggest an interaction between ranibizumab and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines. SARS-CoV-2 vaccines may be administered to patients at any time during the study. The vaccine should be documented on the concomitant medication eCRF. SARS-CoV-2 vaccines should be given in accordance with the approved vaccine label.

4.4.1 Permitted Therapy

Patients who use maintenance therapies should continue their use unless prohibited as indicated in Section 4.4.2.

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

- PRP

  If, at the investigator's discretion, a patient requires PRP for DR progression in the study eye after the screening visit during participation in the study, the investigator *may* discuss the clinical indication with the Medical Monitor; in very specific cases, this therapy may be permitted.

- Cataract surgery in the study eye, if clinically indicated and occurring 7 or more days after the final study treatment, with the next study treatment held for 7 or more days following the surgery

- *YAG laser capsulotomy and selective laser trabeculoplasty in the study eye, if clinically indicated and occurring 7 or more days after the last study treatment, with the next study treatment held for 7 or more days following the procedure*
- Treatment, as clinically indicated, for the onset of increased IOP and/or glaucoma in the study eye
- Use of *topical* nonsteroidal anti-inflammatory drugs (NSAID) for preoperative prophylaxis and *topical* NSAIDs and/or topical corticosteroids post-implant insertion or post-explantation surgery for postoperative healing or as clinically indicated in the study eye (see Appendix 17 for administration schedule)
- Administration of intravitreal ranibizumab 0.3 mg or other approved anti-VEGF as per local regulations, at the discretion of the evaluating investigator, if a patient's fellow eye (non–study eye) requires treatment for any approved indication following screening

  If the fellow eye is to receive treatment, it may be administered at the same visit as the study eye treatment. All study assessments and study eye treatment, should be completed *as specified in the protocol* prior to fellow eye treatment. Individual trays and sterile preparation, as needed, must be separately prepared for each eye.
- Continuous use of aspirin or NSAID treatment, except as outlined below

  All patients receiving ongoing aspirin or NSAID treatment must interrupt aspirin or NSAID treatment for 7 days prior to PDS implant insertion surgery. Interruption of these medications must be pre-planned at the screening visit to avoid delay in implant surgery. These medications can be restarted, if appropriate, after the post-implant insertion Visit 1 occurs. One-time use of aspirin or NSAIDs for pain management after implant insertion is allowed.
- Ongoing anticoagulant or antiplatelet therapy (other than aspirin or other NSAIDs), as outlined below

  Patients who are receiving ongoing anticoagulant or antiplatelet therapy (other than aspirin or other NSAIDs) could be enrolled if they can safely and are willing to temporarily interrupt these medications prior to the Week 4 implant insertion visit (PDS arm) or Week *64* implant insertion visit (comparator arm), respectively, after discussion with their prescribing physician. Oral anticoagulants include vitamin K antagonists (e.g., warfarin), direct factor Xa inhibitors (e.g., rivaroxaban, apixaban, edoxaban, fondaparinux), and direct thrombin inhibitors (e.g., dabigatran). Antiplatelet therapies include*, but are not limited to,* clopidogrel, prasugrel, dipyridamole, ticagrelor, and ticlopidine. The duration of the treatment interruption period should be deferred to the investigator in consultation with the prescribing physician and should be made on the basis of the risks of oral anticoagulant or antiplatelet therapy weighed against potential benefits and in consideration of the medication's prescribing information. Interruption of these medications must be pre-planned at the screening visit and again prior to randomization to avoid delay in implant

surgery. These medications can be restarted after the post-implant insertion Visit 1 occurs.

- Conditional use of magnetic resonance imaging (MRI) scans for patients with the PDS

  A patient with the PDS *implant* can be safely scanned in an MRI system meeting the following conditions:

  - Static magnetic field of 1.5-Tesla (1.5 T) or 3-Tesla (3T)
  - Maximum spatial field gradient of 3,000 G/cm (30 T/m)
  - Maximum MRI system reported, whole-body-averaged specific absorption rate (SAR) of 4.0 W/kg (First Level Controlled Operating Mode)
  - For additional information, refer to the PDS IFU document.

4.4.2 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below at any time during the study:

- Concurrent use of any systemic anti-VEGF agents
- Concurrent treatment with anti-VEGF agents (other than the protocol-specified treatments) in study eye
- Concurrent use of intravitreal corticosteroid or corticosteroid implants (e.g., Ozurdex®, Illuvien®) in study eye
- *Concurrent use of chronic topical (ocular) corticosteroids in the study eye*
- Concurrent use of periocular (subtenon) corticosteroids (except corticosteroid solutions [not corticosteroid suspensions] at conclusion of PDS implant insertion or explantation surgery, *or other PDS-related ocular procedures*) in *study eye*
- *Concurrent use of suprachoroidal corticosteroids (e.g., Xipere) in the* study eye
- Administration of micropulse and focal or grid laser in study eye
- Concurrent treatment with Visudyne® (verteporfin injection) in study eye
- Concurrent use of and participation in other studies for experimental therapies (except those with minerals and vitamins)

If a patient receives any of the above listed treatments at any time during the study, the Sponsor will determine if discontinuation of the study treatment is required.

4.5 STUDY ASSESSMENTS

The schedules of activities to be performed during the study are provided in Appendix 1, Appendix 2, and Appendix 3. All activities should be performed and documented for each patient.

4.5.1 Informed Consent Forms and Screening Log

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

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a *detailed* record of all patients screened and to *document* eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements), including pre- and post-treatment antimicrobial and anti-inflammatory medications, used by the patient within 7 days prior to the randomization/Day 1 study visit will be recorded. Protocol-specified procedural medications administered at the site (e.g., dilating drops, fluorescein dyes, implant insertion, refill-exchange and explantation procedure medications) will not be recorded. At the time of each follow-up study visit, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

History of anti-VEGF medications administered to the patient's fellow eye prior to the screening visit will be recorded.

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

4.5.3 Vital Signs

Vital signs will include measurements of pulse and systolic and diastolic blood pressure while the patient in a seated position after resting for 5 minutes. Height and weight measurement will be recorded at screening visit only.

4.5.4 Ocular Assessments

Ocular assessments include the following and will be performed for both eyes except where noted and at specified timepoints according to the schedules of activities in Appendix 1, Appendix 2, and Appendix 3:

- BCVA assessed on ETDRS chart at a starting distance of 4 meters (perform prior to dilating eyes; see Appendix 7)
- IOP measurement

At each visit perform IOP measurement prior to dilating pupils, and prior to intravitreal ranibizumab injection or refill-exchange procedure when applicable. The method used for a patient must remain consistent throughout the study for visits in the office.

- Slitlamp examination (for grading scales for anterior *chamber flare or cells,* vitreous cells and vitreous hemorrhage density, see Appendix 8) including *external* inspection of the conjunctiva (elevation of the upper eyelid is recommended to allow inspection of conjunctiva in superior quadrants*), and dilated slit-lamp examination of the implant in the vitreous cavity through the pupil to monitor implant placement and to evaluate any other implant-related problems*
- Dilated binocular indirect high-magnification ophthalmoscopy

  Dilated binocular indirect ophthalmoscopy examinations will be performed in the study eye at the following visits in order to monitor implant placement and to evaluate other potential implant-related problems:

  - *After implant and new implant insertion and 1 day and 7 (±2) days post-implantation*
  - *Prior to and after completing refill-exchange procedure*
  - *At each visit after implantation*
- Finger-counting test followed by hand motion and light perception tests (when necessary) performed within 15 minutes of post-study treatment in the study eye only.

Patients will remain at the surgical center after PDS implant insertion and will remain in the office after refill-exchange until the designated physician has assessed that there are no safety concerns following treatment, at which point the patient will be allowed to leave. If any safety concerns or immediate toxicity is noted, the patient will remain at the surgical center and will be treated according to the designated physician's clinical judgment. If applicable, the adverse event and the adverse event treatment and other relevant information 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 PDS implant surgical procedures, regardless of whether a safety event occurred in a particular patient or not. Results of the additional ocular assessments will be forwarded to the Sponsor for evaluation and/or storage.

4.5.5 Ocular Imaging

A central reading center will provide sites with the central reading center manual and training materials for specified study ocular images. Before any study images are obtained, site personnel, test images, systems, and software (where applicable) will be certified and validated by the reading center as specified in the central reading center manual. All ocular images will be obtained by trained site personnel at the study sites, will be forwarded to the central reading center for independent analysis and/or storage, and will later be transferred to Roche.

Note: Between randomization and Week 88, if a patient misses a study visit when ocular images are scheduled (see Appendix 2 and Appendix 3), the images should be obtained at the next scheduled visit the patient attends. If a patient misses a visit at Week 88 or later, patients should return to the clinic to complete imaging assessments within 4 weeks.

The following ocular images of both eyes (unless noted otherwise) will be collected from all study patients, according to the reading center image acquisition protocol:

- Lens photographs (fundus reflex photographs; see Appendix 10)
- CFP (see Appendix 10)

  Note: CFP must be performed using standard 7-modified field protocol or 4-wide field protocol for all patients at all sites. For sites that have ultra-widefield (UWF; Optos®) fundus imaging available, an additional, optional singular UWF CFP image may be submitted at the same timepoints as protocol-required CFP (see central reading center manual).
- FA images (to be performed after laboratory samples are obtained; see Appendix 11)

  Note: See central reading center manual for acceptable image acquisition protocols and devices. The same field of view must be used for all visits from each individual patient.
- SD-OCT scans (see Appendix 12)

  Note: Central subfield thickness (CST) is defined as the average thickness of the central 1 mm circle of the ETDRS grid centered on the fovea from inner limiting membrane to Bruch's membrane (see central reading center manual).

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

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

  Implant photographs can be obtained after application of topical fluorescein to the surface of the eye over the implant to monitor conjunctiva (e.g., if suspected conjunctival erosion).

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

- OCT-*angiography* images at sites with *OCT-angiography capabilities (see* Appendix 14*)*

The following ocular images of the study eye will be collected from study patients using anterior segment OCT (AS-OCT), including optional AS-OCT angiography, and will

be performed on the study eye only at selected study sites or at sites per investigator discretion that have this imaging capability. All images will be forwarded to the central reading center for evaluation and/or storage, and will later be transferred to Roche:

- *AS-OCT, including optional AS-OCT angiography images at sites with imaging* capabilities (see Appendix 15)

Additional details on obtaining these images are included in the central reading center manual.

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

Ocular images collected from study patients will be evaluated using advanced analytics tools (e.g., artificial intelligence-based algorithms) to assess progression to visual-threatening presentations of DR, in order to evaluate the performance of the tool and not for treatment decisions in the study.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

At a given visit, specimens should be obtained prior to study eye treatment and FA assessments (if applicable). Fasting is not required prior to specimen collection.

Samples will be shipped to a central laboratory and/or the Sponsor or a selected designee for analysis and/or storage. All instructions for obtaining, processing, storing, and shipping specimens are provided in the laboratory manual. Laboratory supply kits will be provided to the sites by the central laboratory. See Appendix 2 and Appendix 3 for sample collection timepoints and Appendix 16 for biological sample collection and shipping instructions. All samples obtained during screening from patients who are not randomized will be discarded.

The following assessments will be performed:

- Hematology: hemoglobin, hematocrit, quantitative platelet count, RBCs, WBCs, and differentials, including neutrophils, bands, lymphocytes, basophils, eosinophils, and monocytes (absolute and percent)
- Serum chemistry: glucose, creatinine, total and direct bilirubin, total protein, albumin, AST, and ALT
- HbA_{1c}

  Note: For HbA_{1c}, the most recent historical (within 2 months of screening) or locally obtained laboratory results may be used for screening.
- Urinalysis: protein, ketones, glucose, bilirubin, and urobilinogen
- Coagulation: aPTT and PT

- Aqueous humor samples for measurement of biomarkers and/or ranibizumab concentration
- Serum samples for measurement of ADAs
- Serum samples for measurement of ranibizumab concentration
- Serum pregnancy test (if required)

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

- Pregnancy test

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

The following samples will be *sent to the Sponsor or its designee and/or to a central laboratory for analysis* from patients *treated* with the PDS *only* and may be analyzed in the future:

- Explanted implant with contents (explanted implant containing a mixture of ranibizumab drug product, *intraocular fluid,* and vitreal components diffused into the implant), preserved for potential analysis upon explant procedure
- *Refill-exchange needle with contents (containing a mixture of ranibizumab drug product, intraocular fluid, and vitreous diffused into the implant) as required*

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

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

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.10), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- *S*amples for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Aqueous humor and plasma samples collected for biomarker research will be destroyed no later than 15 years after the final Clinical Study Report has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the

samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

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

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

4.5.7 Patient Treatment Experience Assessments

The patients' perspective on their treatment experience will be captured through two questionnaires: the *PDS Patient Preference Questionnaire* (PPPQ) and the *Retinopathy Treatment Satisfaction Questionnaire, status version* (RetTSQs).

Questionnaires will be interviewer-administered by site personnel (other than the BCVA examiner) prior to any other visit assessments or procedures being performed. Interviews will be conducted using versions of the questionnaire translated and linguistically validated into the local language of the patient. Patients may be excluded from completing these assessments if a translation is not available in their spoken language.

4.5.7.1 Port Delivery System Patient Preference Questionnaire

The PPPQ is a 3-item questionnaire that captures a patient's preference for treatment, the strength of their preference, and the reasons for their preference (Tschosik et al. 2019). The PPPQ was developed from patient preference questionnaires in the literature and modified for use with the PDS (Pivot et al. 2013; Rummel et al. 2017). The PPPQ will be administered only to patients who have experience with both PDS and intravitreal ranibizumab injections.

4.5.7.2 Retinopathy Treatment Satisfaction Questionnaire

The RetTSQs is a 14-item questionnaire designed to assess treatment satisfaction in patients with retinopathy, including satisfaction with positive aspects of treatment and negative aspects of treatment. The total score ranges from 0 to *78*, with a higher score indicating greater satisfaction (Brose and Bradley 2009).

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

The PDS implant insertion, explantation, refill-exchange, and any other ocular PDS-related procedures (e.g., conjunctival erosion or retinal detachment repair) performed in the study eye will be captured on video unless the study center has policies in place that prohibit these procedures from being video captured. Recordings may be used for, but

are not limited to, physician training or product characterization and may be forwarded to a central reading center for analysis and/or storage and will be later transferred to Roche.

4.5.9 Optional Aqueous Humor and Blood Samples

Identification of biomarkers that improve our ability to identify patients with NPDR who are at significant risk of developing PDR/ASNV or clinically significant CI-DME is essential for optimal disease management. Identification of additional factors contributing to DR progression is warranted, as this may lead to the future development of new therapeutic targets. Therefore, for consenting patients in the comparator arm, optional aqueous humor and blood samples will be collected at Day 1 and Q24W thereafter, as specified in Appendix 2 and Appendix 3, to identify novel biomarkers that are prognostic for DR progression to more severe states as well as biomarkers that correlate with disease severity.

For patients in the PDS arm, as well as for patients in the comparator arm rolling over to the PDS, optional aqueous humor and blood samples will be collected as specified in Appendix 2 and Appendix 3 to better understand the relationship between ocular VEGF levels and duration of treatment efficacy, as well as to better understand variability in patient responses to ranibizumab treatment.

Aqueous humor sample cap for the PDS arm:

- A maximum of four aqueous humor samples may be collected per refill-exchange interval (defined as the period beginning at either implant insertion or refill-exchange and ending at the visit prior to the next subsequent scheduled refill-exchange, i.e., implant insertion to Week 36; Week 40 to Week 72, etc.) either from an aqueous humor sample collection outlined in Appendix 2 or Appendix 6.

Aqueous humor sample cap for the comparator arm:

- **Prior to receiving PDS implant:**
- A maximum of five aqueous humor sample collections may be performed prior to the PDS implantation visit (i.e., randomization to Week 60) either from an aqueous humor sample collection outlined in Appendix 3 or Appendix 6.

After PDS has been implanted:

- A maximum of four aqueous humor samples may be collected per refill-exchange interval (i.e., from implant insertion Week 64 to Week 88, etc.) after PDS has been implanted, either from an aqueous humor sample collection outlined in Appendix 3 or Appendix 6.

Samples may be used for exploratory biomarker research as described in Section 4.5.6. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. Refer to Section 4.5.6 for details on duration of sample storage, use

of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.10 Optional Samples for Research Biosample Repository

4.5.10.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

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

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

4.5.10.2 Approval by the Institutional Review Board or Ethics Committee

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

4.5.10.3 Sample Collection

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

- Blood sample collected at randomization
- Leftover blood, serum, plasma, and aqueous humor samples, and any derivatives thereof (e.g., DNA, RNA, proteins, peptides), performed at the investigator's discretion during the course of the study

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

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

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

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

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

4.5.10.4 Confidentiality

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

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

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

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

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

4.5.10.5 Consent to Participate in the Research Biosample Repository

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

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

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

4.5.10.6 Withdrawal from the Research Biosample Repository

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

global.rcr-withdrawal@roche.com

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

4.5.10.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review,

and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy

Patients may be permanently discontinued from study treatment if they experience any of the following:

- Observed damage to the implant
- Any treatment for DR with or without DME not specified in the protocol

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

Patients with septum dislodgement who elect not to undergo explantation or new implant insertion will be discontinued from study treatment (no additional refill-exchange procedures will be performed). These patients will be eligible to receive Sponsor-provided intravitreal ranibizumab 0.3 mg treatment as per local label and regulations and per the clinical judgment of the investigator following consultation with the Medical Monitor.

Upon study treatment discontinuation, patients with the PDS implant will no longer undergo refill-exchange procedures. Patients in the comparator arm will not receive the PDS implant if study participation is discontinued before Week 64.

All patients who discontinue study treatment but remain participating in the study will be encouraged to attend as many scheduled study visits as possible, with an emphasis on Week 52 and the final study visit (see Appendix 5 for the minimum required assessments to be performed). Per investigator judgment, patients may start treatment for DR with or without DME in the study eye per standard of care not specified in the protocol, after the decision to discontinue study treatment has been made. Sponsor-provided intravitreal ranibizumab 0.3 mg treatment as per local label and regulations will be available for patients who discontinue from the PDS study treatment but remain participating in the study, for both study eye and fellow eye treatments, if the anti-VEGF chosen by the investigator is ranibizumab.

The investigator must notify the Medical Monitor if the decision to perform explantation is made after study treatment discontinuation. Explanted patients will return for safety assessments at 1, 7 (±2), 30 (±7), and 60 (±7) days post-explantation (see Appendix 5). Patients can remain in the study after their final post-explantation safety visit. They can return for as many scheduled study visits as possible (with an emphasis on completing the Week 52 and final study visits) and remain eligible to receive Sponsor-provided intravitreal ranibizumab 0.3 mg for the study eye and the fellow eye (as clinically indicated per standard of care in accordance with label and local regulations) once the need for explantation is confirmed, and preferably after explantation is completed, if possible.

4.6.2 Patient Discontinuation from Study

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

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

  If a patient misses more than two consecutive visits prior to PDS implant insertion or within any 36-week treatment period, the investigator and the Sponsor may consider withdrawing the patient from the study.
- Investigator or Sponsor determination that it is in the best interest of the patient
- If patient cannot undergo PDS implantation by Week 8 (PDS arm) or Week 68 (comparator arm).

Patients who withdraw from the study prematurely before receiving the PDS implant should return for an early termination evaluation visit 30 (+7) days following the final study visit for monitoring of all adverse events (serious and non-serious) and early termination assessments (see Appendix 2).

Patients with the PDS who withdraw from the study prematurely but do not undergo explantation to remove the PDS implant will be scheduled for an early termination evaluation visit at 90 (+7) days after the implant insertion procedure for monitoring of all adverse events (serious and non-serious). If the patient withdraws after 90 days from receiving the implant, they will be scheduled for an early termination visit 30 (+7) days following their final completed study visit (see Appendix 2 and Appendix 3).

Patients with the PDS who choose to withdraw from the study prematurely and choose to undergo explantation to remove the PDS implant will be followed for approximately

90 days after explantation, encompassing the following visits: safety assessments at 1, 7 (±2), 30 (±7), and 60 (±7) days post-explantation (see Appendix 5), and an early termination evaluation visit 30 (+7) days after the final safety assessment. Before the decision to explant is made, the investigator must notify the Medical Monitor. Per investigator judgment, once the need for explantation is confirmed, patients may start intravitreal anti-VEGF treatment for DR with or without DME in the study eye, including Sponsor-provided intravitreal ranibizumab 0.3 mg as per local label and regulations and continue treatment until the early termination visit is completed or the patient withdraws from the study. If possible, intravitreal anti-VEGF treatment should be administered after explantation is completed.

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

4.6.3 Study Discontinuation

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

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

The Sponsor will notify investigators if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The Port Delivery System with ranibizumab (100 mg/mL) with Q24W refill-exchange was approved by the U.S FDA on 22 October 2021 under the tradename

SUSVIMO (ranibizumab injection) for the treatment of patients with nAMD who have previously responded to at least two intravitreal injections of a VEGF inhibitor medication. The safety plan for patients in this study is based on clinical experience with the PDS in completed and ongoing studies. The anticipated important safety risks for PDS are outlined below. Please refer to the PDS Investigator's Brochure for a complete summary of safety information.

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

5.1.1 Safety Assessments

The schedules of safety assessments to be performed during the study are provided in Appendix 1, Appendix 2, and Appendix 3.

Upon completion of the implant insertion procedure at Week 4 (PDS arm) or Week 64 (comparator arm) *or if a new implant is inserted after explantation*, patients will have *dilated* indirect ophthalmoscopy performed to monitor the implant placement and to evaluate any potential implant problems. The treating clinician will check IOP by digital palpation for the study eye only, as clinically indicated. These assessments must be performed prior to placing a patch on the eye after implant insertion. Patients will remain in the surgical center until the designated clinician has assessed that there are no safety concerns following treatment, at which point the patient will be allowed to leave. If any safety concerns are noted, the patient will remain in the surgical center and will be treated according to the designated clinician's clinical judgment. If applicable, the adverse event and treatment of the adverse event will be reported on the appropriate eCRFs, along with other relevant information. Patients who receive the PDS will return for additional safety evaluation visits 1 day (post-implant insertion Visit 1) and 7 days (±2 days) (post-implant insertion Visit 2) after the implant insertion procedure. *After a new implant is inserted after explantation, patients will return for additional safety evaluation visits 1 day (post–re-implant insertion Visit 1), 7 days (±2 days) (post–re-implant insertion Visit 2), and 28 days (±2 days) (post–re-implant insertion Visit 3) (see Appendix 4).*

- The use of self-administered topical antimicrobial and/or anti-inflammatory ophthalmic drops may be required before and/or after PDS implant insertion surgery and/or refill-exchange procedures; see Appendix 17 for the administration schedule. Please note that some ophthalmic drops are given as per investigator's discretion.
- All patients will be contacted by study site personnel 3 (± 1) days after each treatment (refill-exchange or intravitreal injection) to elicit reports of any decrease in vision, eye pain, unusual redness, or any other new ocular symptoms in the study

eye. If applicable, patients will be queried regarding the use of prescribed anti-inflammatory and anti-microbial ophthalmic drops.

Patients will also be asked whether they have taken the prescribed, self-administered, pre- and post-treatment anti-inflammatory and antimicrobial ophthalmic drops (if applicable) for their study eye as directed by the investigator. All patients will be instructed to contact the site at any time if they have any health-related concerns. If warranted, patients will be asked to return to the clinic as soon as possible for an unscheduled safety assessment visit (see Appendix 5).

A finger-counting test will be conducted for each patient within 15 minutes following study treatment (refill-exchange or intravitreal injection); hand motion and light perception tests will be performed when necessary within 15 minutes following study treatment.

Detailed ocular examinations, including indirect ophthalmoscopy and slitlamp examination, will be performed throughout the study. A careful examination of the implant and surrounding tissue using the slitlamp should be performed at each study visit. All patients will undergo dilated binocular indirect high-magnification ophthalmoscopic examination at each visit, which will include visual monitoring of the implant placement and evaluation of any other implant-related problems, as well as data collection on the associated eCRFs. The sample content retrieved during explantation procedures will be collected and forwarded for analysis to the Sponsor or its designee, and/or to a central laboratory and may be analyzed in the future.

Refill-exchange procedure will be interrupted or discontinued per the criteria listed in Table 1 and at the investigator's discretion if there are any suspected safety or other treatment-related issues. If the investigator decides to interrupt a dose, the reason will be recorded on the corresponding eCRF and, if appropriate, on the Adverse Event eCRF. In the event a patient experiences an adverse event in the study eye that is considered by the investigator to be severe in intensity or serious in nature, consideration should be given to interrupting the treatment or discontinuing the patient from study drug treatment or the study. The decision will be at the investigator's discretion and should be recorded on the eCRF. See Sections 4.6.1 and 4.6.2 for information on study treatment discontinuation and patient discontinuation from the study, respectively.

Patients who are discontinued from the study prior to completion of the study treatment period (see Section 3.2) will be asked to return for early termination visit assessments (see Section 4.6.2). The visit will include assessment of all adverse events (serious and non-serious; ocular and non-ocular). All adverse events (serious and non-serious) will be recorded on eCRFs for the duration of this study. Serious adverse events will be reported in compliance with Good Clinical Practice guidelines.

An iDMC will monitor safety and study conduct on an ongoing basis (see Section 3.1.6 for details).

5.1.2 Anticipated Risks Associated with Port Delivery System with Ranibizumab Implant and/or *Its* Procedures

5.1.2.1 Vitreous Hemorrhage

The PDS implant and/or its procedure has been associated with vitreous hemorrhage. These events may be clinically relevant and may result in temporary vision loss. Surgical intervention (i.e., vitrectomy) may be needed in the case of a non-clearing vitreous hemorrhage. *Follow the recommended management guidelines in Section* 5.1.5.3. Patients on anti-thrombotic medication may be at increased risk of vitreous hemorrhage. Anti-thrombotics must be temporarily interrupted prior to the implant insertion procedure.

Close adherence to the most up-to-date PDS IFU document (e.g., appropriate pars plana laser ablation, scleral cauterization, etc.) is required to minimize risks of surgery and implant insertion–related vitreous hemorrhage.

5.1.2.2 Conjunctival Bleb

The PDS implant and/or its procedures have been associated with adverse events of conjunctival bleb (defined as encapsulated elevation of the conjunctival tissue above the implant flange, which may be secondary to subconjunctival thickening or fluid). These events may be clinically relevant and may require additional medical and/or surgical management to avoid further complications, especially if the implant septum is no longer identifiable due to conjunctival bleb. *Follow the recommended management guidelines in Section* 5.1.5.5.

Close adherence to the most up-to-date PDS IFU document (e.g., appropriate scleral incision length, appropriate incorporation of conjunctiva and Tenon's capsule in peritomy closure, appropriate seating of the refill needle during refill-exchange procedure, etc.) is required to minimize risks of conjunctival bleb.

5.1.2.3 Conjunctival Erosion

The PDS implant and/or its procedures have been associated with conjunctival erosion (defined as a full thickness degradation or breakdown *of* the conjunctiva). These events may be clinically relevant, especially if the implant becomes exposed, and could be associated with an increased risk of endophthalmitis. The tissue overlying the PDS implant flange should be monitored carefully following the implant insertion and refill-exchange procedures to identify early signs of erosion and permit early medical or surgical intervention if necessary. *If conjunctival erosion occurs, follow the recommended management guidelines in Section* 5.1.5.4. After discussion with the Medical Monitor, surgical intervention (e.g., conjunctival/Tenon's capsule repair) should be performed in case of conjunctival erosion with or without exposure of the implant flange.

Close adherence to the most up-to-date PDS IFU document (e.g., appropriate incorporation of conjunctiva and Tenon's capsule in peritomy closure, appropriate placement of conjunctival sutures to avoid contact with the implant edge, etc.) is required to minimize risks of surgery/implant insertion-related conjunctival erosion.

5.1.2.4 Conjunctival Retraction

The PDS implant and and/or its procedures have been associated with adverse events of conjunctival retraction (defined as a recession or opening of the limbal and/or radial peritomy). These events may be clinically relevant, especially if the implant becomes exposed, and could be associated with an increased risk of endophthalmitis. The tissue overlying the PDS implant flange should be monitored carefully following the implant insertion and refill-exchange procedures to identify early signs of retraction, and permit early medical or surgical intervention if necessary. *If conjunctival erosion occurs, follow the recommended management guidelines in Section* 5.1.5.4.

After discussion with the Medical Monitor, surgical intervention (e.g., conjunctival/Tenon's capsule repair) should be performed in case of conjunctival retraction with or without exposure of the implant flange.

Close adherence to the most up-to-date PDS IFU document (e.g., including appropriate suturing of conjunctiva and Tenon's capsule to the limbus, etc.) is required to minimize risks of conjunctival retraction.

5.1.2.5 Rhegmatogenous Retinal Detachment

The PDS implant and/or its procedures have been associated with rhegmatogenous retinal detachment. These events are clinically relevant and may result in vision loss if not promptly treated with an intervention (e.g., pneumatic retinopexy, vitrectomy, or laser photocoagulation). Careful evaluation of the retinal periphery by *360 degree* scleral indentation should be performed, and any suspected areas of abnormal vitreo-retinal adhesion or retinal breaks should be treated before inserting the implant in the eye.

Close adherence to the most up-to-date PDS IFU document (e.g., appropriate management of vitreous prolapse after pars plana incision, etc.) is required to minimize risks of rhegmatogenous retinal detachment.

5.1.2.6 Endophthalmitis

The PDS implant and/or its procedures have been associated with endhophthalmitis. These events are clinically relevant, and require prompt treatment as per standard of care to reduce risk of vision loss and maximize recovery (e.g., intravitreal vancomycin and ceftazidime, as well as topical and/or oral antibiotic drops, for bacterial endophthalmitis). *Preservative-free saline* flush of the implant content using the refill needle, followed by implant flush with 100 µL vancomycin (1.0 mg/*0.1* mL) may also be performed as additional treatment. *Follow the recommended management guidelines in Section* 5.1.5.6.

Close adherence to the most up-to date PDS IFU document (e.g., appropriate sterile controls during implant insertion or refill-exchange procedures, etc.) is required to minimize risks endophthalmitis. *In addition, appropriate conjunctiva management and early detection with surgical repair of conjunctiva retractions or erosions may reduce the risk of endophthalmitis. Follow the recommended management guidelines in Section 5.1.5.4 and Section 5.1.5.5.*

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

5.1.2.7 Device Dislocation

The PDS implant and/or its procedures have been associated with device dislocation. The implant may dislocate or subluxate into the vitreous cavity, or may extend outside the vitreous cavity into or beyond the subconjunctival space. These events are clinically relevant and in some cases may require urgent surgical intervention to prevent vision loss. *If device dislocation occurs, follow the recommended management guidelines in Section 5.1.5.7.* After discussion with the Medical Monitor, urgent surgical intervention should be performed if device dislocation is associated with a positive Seidel test, retinal detachment, appositional choroidal detachment, dislocated implant resting on or near the macula, conjunctival opening with vitreous leak and implant expulsion (open globe).

Close adherence to the most up-to-date PDS IFU document (e.g., appropriate scleral incision length, appropriate targeting of the pars plana during laser ablation, etc.) is required to minimize risks of device dislocation.

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

5.1.2.8 *Septum Dislodgement*

Septum dislodgement is a device deficiency during which the septum (a component of the implant that ensures self-sealing) has dislodged into the implant body (see Figure 2). Although the silicone overmold covering the top of the device can remain in place, the self-sealing properties of the device are impaired. In the presence of septum dislodgement, normal device functioning cannot be assured. Septum dislodgement has been observed after refill-exchange procedures. These events are clinically relevant and may require additional medical and/or surgical management. Careful examination of the implant in the vitreous cavity through the dilated pupil is required prior to and after the refill-exchange procedure to check the appearance of the implant and its components.

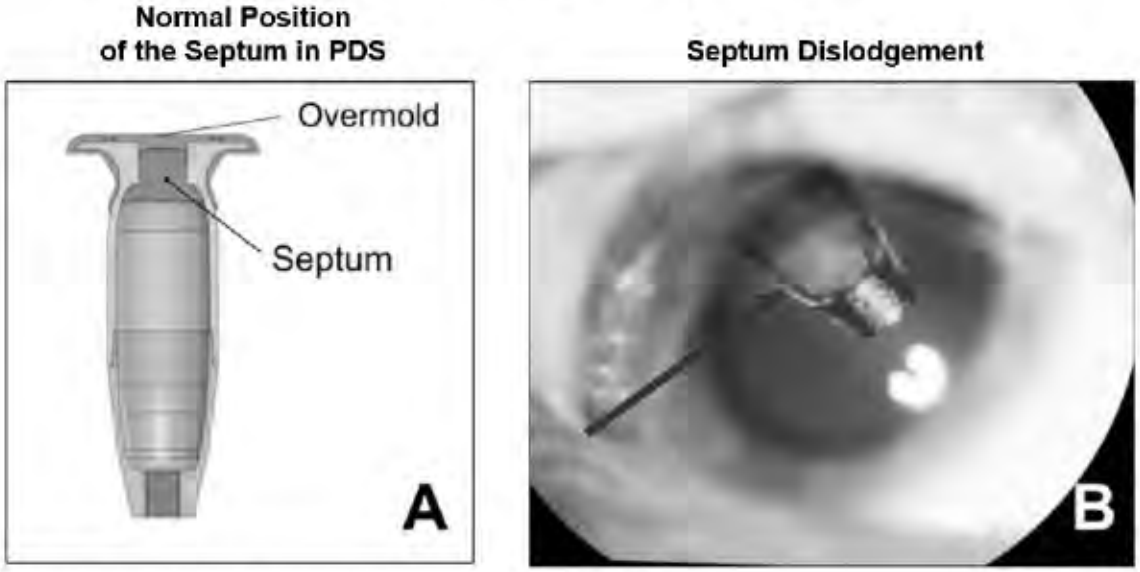
If septum dislodgement is suspected or occurs, follow the recommended management guidelines in Section 5.1.5.8. Do not perform the refill-exchange procedure because normal device functioning cannot be assured.

To minimize risks of septum dislodgement, close adherence to the most up-to-date PDS IFU document is required, including the following instructions for insertion of the refill needle during a refill exchange procedure:

- *If excessive resistance, withdraw the refill needle with gentle counter pressure with a moist cotton swab, orient and insert again.*
- *Do not twist when encountering conjunctiva and Tenon's capsule to gain access to the septum, as damage to the overlying tissue and to the septum of the device may result.*

Refer to the PDS Investigator's Brochure for further information.

Figure 2 Visual Representation of (A) Normal Position of the Septum in PDS Compared with (B) Septum Dislodgement



PDS =Port Delivery System with ranibizumab.
Source: Image A: technical data on file (SRD-0141250); Image B: clinical data on file.

5.1.3 Risks Associated with Intravitreal Ranibizumab Injection

5.1.3.1 Increased Intraocular Pressure

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

5.1.3.2 Cataract

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

5.1.3.3 Intraocular Inflammation

Intraocular inflammation can range from a mild to severe inflammation of the eye with sequelae that may lead to vision loss. Inflammation can occur due to potential immunogenicity, in reaction to the active substance or its excipients, or in*flammatory* response *due* to the invasive nature of the procedure. It is also hypothesized that intravitreal *ADA response may* contribute to the development of intraocular inflammation; however, there is currently no evidence either from the published literature or from the postmarketing data to support this assertion. There is potential introduction of microorganisms during the injection procedure, as described in Section 5.1.3.5 (endophthalmitis).

5.1.3.4 Retinal Detachment and Retinal Tear

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

5.1.3.5 Endophthalmitis

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

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

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

5.1.4.1 Glaucoma

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

5.1.4.2 Venous Thromboembolic Events

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

5.1.4.3 Non-Myocardial Arterial Thromboembolic Events

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

5.1.4.4 Myocardial Infarction

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

5.1.4.5 Non-Ocular Hemorrhage

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

5.1.4.6 Hypertension

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

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

5.1.5 Management of Patients Who Experience Adverse Events

5.1.5.1 Dose Modifications

No dose modifications will be permitted in this study.

5.1.5.2 Treatment Interruption

Study treatment dose interruption and/or study treatment discontinuation or study discontinuation following an adverse event will be determined according to the criteria in Table 1. The investigator should contact the Medical Monitor if the study treatment dose is interrupted and delay of treatment is to be considered for conditions outside of those specified in Table 1. The reason for interrupting the treatment should be recorded on the associated eCRF and, if applicable, on the Adverse Event eCRF.

Table 1 Dose Interruption, Study Treatment Discontinuation, or Study Discontinuation Criteria

Event	Dose Interruption Criteria
Intraocular inflammation	Interrupt dose if intraocular inflammation is ≥2+ in the study eye (see the definitions of intraocular inflammation in Section 5.1.3.3). Study treatment may be delayed or the patient may be discontinued from study treatment after consultation with the Medical Monitor.
BCVA decrease	Interrupt dose if there is a study drug–related decrease of ≥30 letters in BCVA in the study eye compared with the last assessment of BCVA.
Elevated IOP	Interrupt ranibizumab study treatment via intravitreal injection if pre-treatment IOP in the study eye is ≥30 mmHg. Treatment will be permitted when IOP has been lowered to <30 mmHg, either spontaneously or by treatment, as determined by the investigator. Note: For patients with the PDS, if IOP in the study eye is ≥30 mmHg at a refill-exchange visit, study treatment may proceed if the implant is seated in correct position.
Retinal break or rhegmatogenous retinal detachment or macular hole Stages 3 or 4	Interrupt dose if a retinal break is present in the study eye. Treatment may be resumed ≥28 days after the retinal break has been successfully treated. Patients with a rhegmatogenous retinal detachment or Stage 3 or 4 macular holes may require discontinuation from study treatment after consultation with the Medical Monitor.
Local or systemic infection	*Per clinical judgment, interrupt* dose if *an active infectious eye disease is present in either eye, including* the following: infectious conjunctivitis, infectious keratitis, infectious scleritis, or endophthalmitis in either eye. *Study treatment must* be interrupted if the *investigator determines that there* is a suspected or confirmed severe systemic infection per clinical judgment (including COVID-19). Study treatment may be subsequently permitted after *consultation* with the Medical Monitor.
Intraocular surgery	Dose may be interrupted after consultation with the Medical Monitor if intraocular surgery (except cataract, see Section 4.4.1) has been performed in the study eye within the previous 28 days.
Observed *abnormality* to the *conjunctiva (e.g., conjunctival erosion, retraction, bleb)*	*Interrupt dose if surgical intervention is needed. Please refer to Sections 5.1.5.4 and 5.1.5.5 for recommended management. If study treatment is required per protocol, it may be performed at the time of surgical intervention or as soon as the conjunctival abnormality has resolved.*

BCVA =best-corrected visual acuity; IOP =intraocular pressure; PDS =Port Delivery System with ranibizumab.

Table 1 Dose Interruption, Study Treatment Discontinuation, or Study Discontinuation Criteria *(cont.)*

Event	*Dose Interruption Criteria*
Observed damage to the implant	• *If damage to the implant or to any of its components is observed by the investigator, the implant may be explanted even if it did not cause any adverse event to the patient. The patient may be discontinued from the study treatment.* • *In case of septum dislodgement, the patient may receive a new implant following consultation with the Medical Monitor.*
Pregnancy	*Discontinue patient's study treatment in the case of positive serum pregnancy test during the study. For patients with the PDS, a saline flush of implant contents may be performed to remove active drug from the implant, following consultation with the Medical Monitor.*

BCVA = best-corrected visual acuity; IOP = intraocular pressure; PDS = Port Delivery System with ranibizumab.

5.1.5.3 Recommended Management of Vitreous Hemorrhage

The recommended management of patients with vitreous hemorrhage is presented in Table 2.

Table 2 Recommended Management of *Patients with* Vitreous Hemorrhage

Timing	Patient's Examination and Management Guidelines
Day of vitreous hemorrhage diagnosis	• If the view through the vitreous cavity is limited, if possible, perform ocular B-scan ultrasonography to evaluate areas of the retina not directly visualized on examination, in addition to the assessments scheduled for that specific visit. • A safety assessment visit (scheduled or unscheduled) should be performed approximately 2 weeks after occurrence of vitreous hemorrhage (see Appendix 5). If possible, perform ocular B-scan ultrasonography if the view through the vitreous cavity is limited, to evaluate areas of the retina not directly visualized on examination.
Approximately 4 weeks after occurrence (scheduled visit)	• If possible, perform ocular B-scan ultrasonography if the view through the vitreous cavity is limited in addition to the assessments scheduled for that specific visit, to evaluate areas of the retina not directly visualized on examination. • An unscheduled safety assessment visit should be performed between 4 and 8 weeks after occurrence of vitreous hemorrhage (see Appendix 5).
Approximately 8 weeks after occurrence (scheduled visit)	• If possible, perform ocular B-scan ultrasonography if the view through the vitreous cavity is limited, to evaluate areas of the retina not directly visualized on examination. • If vitreous hemorrhage causes loss in BCVA and neither assessment of the macula nor SD-OCT can be performed successfully: Discuss with the patient the possibility of performing a pars plana vitrectomy to remove the vitreous hemorrhage, *following* consultation with the Medical Monitor.

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

5.1.5.4 Recommended Management of Conjunctival Retraction or Conjunctival Erosion

The recommended management of patients with conjunctival retraction or conjunctival erosion is presented in Table 3.

Table 3 Recommended Management of Patients with Conjunctival Retraction or Conjunctival Erosion

Event	Patient's Examination and Management Guidelines
Conjunctival retraction *(either from limbal or radial incision)*	• Prescribe antibiotic drops as per standard of care • Consult *with* the Medical Monitor for management • *In the case of minimal conjunctival retraction (with or without Tenon's capsule), without leakage or without potential risk of device exposure, it is possible to attempt a course of conservative management and observe the retraction.* • *If any of the above are present or there is concern for their development, schedule* for surgery as soon as possible – Perform conjunctival flap revision with robust undermining of the surrounding conjunctiva and Tenon's capsule and release of any traction from previous surgery before advancing healthy tissue to limbus *or before re-approximating margins of a radial opening.* – Suture the flap with multiple interrupted sutures, *including both conjunctiva and Tenon's capsule in the bites and avoiding lage gaps and any tissue tension.* • In case of recurrent conjunctival retraction *or in the presence of a thin conjunctiva*, consider *the* use of a split-thickness corneal graft placed underneath the conjunctiva and Tenon's capsule (if corneal tissue is not available, *consult with the* Medical Monitor on further management). • *Referral to an anterior segment surgeon may be considered.*
Conjunctival erosion	• In case of confirmed or suspect conjunctival erosion, prescribe antibiotic drops as per standard of care. – For a suspected conjunctival erosion, consider application of topical fluorescein over *the* conjunctiva to confirm erosion on *slit lamp* examination with use of cobalt blue light *(Seidel testing). If available, anterior segment (AS-*OCT) imaging *may be considered by the physician to evaluate the tissues on the top* of the *flange.* – *Implant photographs may be captured before and after application of topical fluorescein to the surface of the eye over the* implant *to monitor* conjunctiva. *(e.g., if suspected* conjunctival *erosion).* • Consult with the Medical Monitor for management. • Watch and wait in case of small localized erosion without flange exposure if the surrounding tissue is well adhered to sclera and there is no evidence of an active leak • Schedule for surgery as soon as possible in case of full-thickness erosion (i.e., exposing the flange) or evidence of an active leak with Seidel positivity. – Perform conjunctival flap revision with robust undermining of the surrounding conjunctiva and Tenon's capsule and release of any traction from previous surgery. – Suture the flap with multiple interrupted sutures, *including both conjunctiva and Tenon's capsule in the bites and avoiding large gaps and any tissue tension.* • In case of recurrent conjunctival erosion, consider use of a split-thickness corneal graft placed underneath the conjunctiva and Tenon's capsule (if corneal tissue is not available, consult *with the* Medical Monitor on further management).

5.1.5.5 Recommended Management of Conjunctival Bleb

The recommended management of patients with conjunctival bleb is presented in Table 4.

Table 4 Recommended Management of Patients with Conjunctival Bleb

Timing of Occurrence	Patient Examination and Management Guidelines
After implant insertion surgery	• *For assessment of fluid-filled blebs, perform the Seidel testing of the bleb, preferably with a fluorescein strip.* – *If the bleb is Seidel positive, speak to Medical Monitor about initial conservative management versus potential surgery to revise conjunctiva/Tenon's capsule and sclerotomy.* – *If negative, continue with post-operative topical medications (Appendix 17) and follow regular visit schedule. Additional unscheduled safety visits should be added to observe the patient as deemed clinically necessary.* • *For subconjunctival tissue thickening (tissue-filled blebs), check if the septum is visible before the next scheduled refill-exchange procedure.* • *If the septum does not appear visible, retroilluminiation should be performed by shining a bright light through the dilated pupil towards the implant body.* – *If the implant septum illuminates and becomes sufficiently visible within the bleb, then a refill-exchange can be attempted.* – *If the septum cannot be visualized with these methods, then surgery may be required to revise the conjunctiva and Tenon's capsule before the next refill-exchange can occur. If this is the case, surgival repair should optimally be timed to coincide with a refill-exchange window so that both procedures can be performed simultaneously.*
During a refill-exchange attempt	• *If the visibility of the implant septum is lost, halt the refill-exchange and ensure that the implant has not subluxated or dislocated into the vitreous cavity or the septum has not dislodged within the implant. These should be assessed with slit-lamp examiniation and/or indirect ophthalmoscopy as required to achieve appropriate visualization of the implant.* – *If it is unclear whether the implant has moved from its original position, the refill-exchange should be delayed. Reassess the patient again after approximately 7 days (or later as needed for the bleb to resolve).* – *If implant is subluxated or dislocated, then follow the recommended management on Table 6.* – *If the septum has dislodged within the implant, follow the recommended management in Table 7.*

5.1.5.6 Recommended Management of Endophthalmitis

The recommended management of patients with endophthalmitis is presented in Table 5.

Table 5 Recommended Management of Patients with Endophthalmitis

Event	Patient Examination and Management Guidelines
Endophthalmitis	• *Per standard of care, perform vitreous tap (aqueous humor tap may be considered per investigator's discretion or if no vitreous can be obtained with a needle tap) and send the specimen to your local laboratory for microbiology cultures. It is recommended to perform a Gram Stain (if sufficient fluid), as well as rapid processing for culture (consider aerobic, anaerobic, mycobacterial, and fungal cultures as appropriate). Other tests per standard of care (e.g., PCR) may be considered in case of suspicion of atypical organisms or in case of negative cultures.* • Treat with *standard of care* intravitreal *antibiotics (e.g.,* vancomycin and ceftazidime*)* • For patients with the PDS *implant*, perform *a preservative-free* saline flush of implant contents using *a* refill needle, followed by a flush of the implant with *100 µL (0.1 mL) of* vancomycin (1.0 mg/*0.1 mL*) using *the* refill needle. • Start antibiotic drop coverage per standard of care. Oral *or systemic* antibiotics may also be considered, *per investigator's discretion.* • In certain circumstances a pars plana vitrectomy could be considered, after consultation with the Medical Monitor. • *Closely check if there are signs of conjunctival erosion or retraction associated with endophthalmitis. If yes, then follow the recommended management in* Table 3. • Perform a safety assessment visit (unscheduled; see Appendix 5) daily after occurrence of endophthalmitis until *the* posterior segment of the eye improves with clearance of the vitreous debris. If possible, perform ocular B-scan ultrasonography. • For patients with a PDS implant, perform a *preservative-free saline flush followed by a* refill-exchange procedure (with ranibizumab 100 mg/mL) after endophthalmitis resolves as determined by the investigator and after *consultation* with *the* Medical Monitor.

PCR = polymerase chain reaction; PDS = Port Delivery System with ranibizumab.

5.1.5.7 Recommended Management of Device Dislocation

The recommended management of patients with device dislocation *is presented* in Table 6.

Table 6 Recommended Management of *Patients with* Device Dislocation

Type of Dislocation	Patient Examination and Management Guidelines
Into the vitreous cavity	The implant may dislocate into the anterior vitreous behind the scleral wound, with secondary vitreous fluid leak underneath the Tenon's capsule through the scleral wound. *If available, anterior segment optical coherence tomography may be considered by the investigator to aid visualization of the implant and surrounding tissues.* It is recommended to surgically remove the implant by performing a vitrectomy and implant removal procedure as soon as possible, after consultation with the Medical Monitor. Urgent surgical intervention is recommended if *device* dislocation is associated with the following events: • Positive Seidel test • Retinal detachment • Appositional choroidal detachments Topical, intravitreal, and/or systemic treatment may also be needed per standard of care in case of ocular infections, intraocular inflammation, hypotony, or other associated events. Prophylactic treatment to limit the risk of ocular infections may be needed in some cases.
Outside the vitreous cavity	The implant may entirely dislocate or subluxate outside the vitreous cavity into or beyond the subconjunctival space. Anterior segment- optical coherence tomography imaging, if available, may be considered by the investigator to aid visualization of the implant *flange* and surrounding tissues. It is recommended to surgically intervene as soon as possible, after consultation with the Medical Monitor. • If the implant is subluxated into the subconjunctival space without extrusion through the conjunctiva and part of the implant body is still in the scleral wound, the implant may be seated back into its original position *using the implant insertion tool. Do NOT handle the implant with forceps or tools other than the implant insertion tool as they can damage the implant.* The oversized scleral wound should be sutured to reduce its length to 3.5 mm to provide tight fit of the implant. • If the implant is entirely dislocated into the subconjunctival space, removal of the implant is recommended followed by closure of the scleral wound with non-resorbable sutures. Urgent surgical intervention is recommended if device dislocation is associated with the following events: • Conjunctival opening with vitreous leak and implant expulsion (open globe) • Retinal detachment • Appositional choroidal detachments Topical, intravitreal, and/or systemic treatment may also be needed per standard of care in case of ocular infections, intraocular inflammation, hypotony, or other associated events. Prophylactic treatment to limit the risk of ocular infections may be needed in some cases.

5.1.5.8 *Recommended Management of Septum Dislodgement*

The recommended management of patients with septum dislodgement is presented in Table 7. See Section 5.1.2.8 for a definition of septum dislodgement.

Table 7 Recommended Management of Patients with Septum Dislodgement

Event	*Patient Examination and Management Guidelines*
Septum dislodgement (in the body of the implant)	• *To identify a dislodged septum, use a dilated slit-lamp examination, implant photographs, and/or dilated indirect ophthalmoscopy. Report a septum dislodgement if seen. During slit-lamp examination, ask the patient to look upward and temporally, and inspect the implant inside the vitreous cavity through the dilated pupil. If a septum dislodgement is observed or suspected, obtain implant photographs, and consult the Medical Monitor. If available, consider imaging, such as AS-OCT, to aid visualization of the implant and surrounding tissues.* • *If septum dislodgement is observed or suspected prior to a refill-exchange procedure, do not perform the refill-exchange procedure because normal device functioning cannot be assured after septum dislodgement.* • *Because the patient can no longer undergo the refill-exchange procedure, based on an individual assessment of the benefit–risk and after consultation with the patient, consider the following:* *Leave the PDS implant in, discontinue study treatment, and monitor the patient for signs of disease activity. Per clinical judgment, consider starting treatment with a locally approved intravitreal anti-VEGF.* *Remove the PDS implant after consultation with the patient and after benefit–risk assessment, including, among other considerations, the systemic and ocular risks associated with undergoing an explantation procedure.* *Remove the PDS implant and insert a new implant after consultation with the Medical Monitor.*

AS-OCT=anterior segment optical coherence tomography; PDS=Port Delivery System with ranibizumab; VEGF=vascular endothelial growth factor.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

The investigator is responsible for ensuring that all adverse events whether associated with the study drug (ranibizumab), or PDS device and/or ancillary devices, or study procedures, or other causes (i.e., all adverse events not associated with any of these elements) are recorded on the associated eCRF in EDC. Adverse event definitions are detailed in this section. Adverse events must be reported to the Sponsor in accordance with instructions for methods and timings provided in Sections 5.4–5.6. Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

The following sections will describe the definitions of adverse events used in this study, which include both pharmaceutical product and medical devices. Adverse events associated with device and/or procedures will be described in Sections 5.2.2.1–5.2.2.4. Guidelines for categorizing adverse events are provided in Appendix 18.

5.2.1 Adverse Events (Pharmaceutical Product)

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.6.8 and 5.3.6.9 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test *(e.g., ECG, X-ray)* that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment *(e.g., screening invasive procedures such as biopsies) with exception to comparator arm adverse events reporting criteria as outlined in Section 5.3.1 and Section 5.4.2.*

5.2.2 Adverse Events (Medical Devices)

According to ISO:14155:2020 *and Article 2(58) of E.U. MDR 2017/745*, an adverse event is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including an abnormal laboratory finding) in patients, users or other persons, in the context of a clinical investigation, whether related or not to the investigational medical device and whether anticipated or unanticipated. Therefore the definition includes events related to:

- The investigational medical device.

- The procedures involved (for the purpose of safety reporting, all activities related to the use of a medical device may be considered procedures)
- For persons other than the study patient (for example, users per intended use of the medical device or other persons such as other study site personnel).

5.2.2.1 Adverse Device Effect *(Immediately Reportable to the Sponsor)*

An adverse device effect is defined as any adverse event related to the use of an investigational medical device. This includes:

- Any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation, or any malfunction of the investigational medical device
- Any adverse event resulting from use error or from intentional misuse of the investigational medical device

5.2.2.2 Serious Adverse Device Effect (Immediately Reportable to the Sponsor)

A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event (see Section 5.2.3 for serious adverse event definition). Serious adverse device effects 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 5.4.4 for reporting instructions).

5.2.2.3 Anticipated Serious Adverse Device Effect (Immediately Reportable to the Sponsor)

An anticipated serious adverse device effect is defined as any of the adverse events listed below that occur only in the study eye, is serious, and if causality is suspected to be related to device and/or procedure:

- Vitreous hemorrhage
- Endophthalmitis
- Retinal detachment
- Conjunctival retraction
- Conjunctival erosion
- Conjunctival bleb or conjunctival-filtering bleb leak
- Hyphema
- Cataract
- Device dislocation
- *Septum dislodgement*

Anticipated serious adverse device effects 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 5.4.4 for reporting instructions).

5.2.2.4 Unanticipated Serious Adverse Device Effect (Immediately Reportable to the Sponsor)

An unanticipated serious adverse device effect is defined as any adverse effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the Investigator's brochure. This includes unanticipated procedure-related serious adverse events; that is, serious adverse events occurring during the study procedure that are unrelated to any malfunction or misuse of the investigational medical device.

Unanticipated Serious adverse device effects 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 5.4.4 for reporting instructions).

5.2.3 Serious Adverse Events (Immediately Reportable to the Sponsor)

According to the ICH guideline for Good Clinical Practice, 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 5.3.6.10)
- 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)

According to ISO:14155:2020 and Article 2(58) of E.U. MDR 2017/745, a serious adverse event is an adverse event that led to any of the following:

- *Death*
- *Serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:*
  - *A life-threatening illness or injury*
  - *A permanent impairment of a body structure or a body function*

- *A chronic disease*
- *In-patient or prolonged hospitalization*
- *Medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure of a body function*

- *Fetal distress, fetal death, a congenital abnormality, or birth defect, including physical or mental impairment*

Note: Planned hospitalization for a preexisting condition, or a procedure required by the study protocol, without serious deterioration in health, is not considered a serious adverse event.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe according the adverse event severity scale; 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).

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

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

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.6.6)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Sight-threatening adverse events: An adverse event is considered to be sight-threatening if it is a serious adverse event (as defined in Section 5.2.3) and it meets one or more of the following criteria:

- The adverse event causes a decrease of ≥30 letters in BCVA (compared with the last assessment of BCVA prior to the most recent treatment) lasting more than 1 hour
- The adverse event requires surgical intervention (i.e., conventional surgery, vitrectomy, vitreous tap, or biopsy with intravitreal injection of anti-infective medications, or laser or retinal cryopexy with gas) to prevent permanent loss of sight.
- The adverse event is associated with severe intraocular inflammation (e.g., endophthalmitis, 4+ anterior chamber cell/flare or 4+ cells in the vitreous; see Appendix 8 for intraocular inflammation grading scales).

Note: Adverse events should be reported listing the underlying cause (if known) of the event as the primary event term (see Section 5.3.6.1).

Ocular adverse events of special interest *are* defined as any of the events listed below regardless of whether they occur in the study eye or the fellow eye, in a patient randomized to the PDS arm or the comparator arm, or the adverse event causality (see Section 5.4.2.2):

- Vitreous hemorrhage
- Endophthalmitis
- Retinal detachment
- Conjunctival retraction
- Conjunctival erosion
- Conjunctival bleb or conjunctival filtering bleb leak
- Hyphema
- Cataract
- Device dislocation

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

5.2.5 Device Deficiency

According to ISO:14155:2020 and Article 2(59) of E.U. MDR 2017/745, a device deficiency is defined as any inadequacy with respect to labeling, identity, quality, durability, reliability, usability, safety, or performance of an investigational device, including malfunctions, use errors, or inadequacy in information supplied by the manufacturer. All device deficiencies must to be recorded *on* the associated eCRFs in EDC. The device deficiency should be assessed for whether or not it is associated with any adverse event, and also assessed for whether the device deficiency could have led to a serious adverse event if a) appropriate action had not been taken, or b) intervention had not occurred, or c) circumstances had been less fortunate.

Any device deficiency that *led to or* could have led to a serious adverse event, as described above, must be reported immediately (i.e., no more than 24 hours after learning of the event). *See the Device Deficiencies and Study Drug Complaints Manual for Clinical Sites for further details.*

5.2.6 Serious Health Threat (Immediately Reportable to the Sponsor)

A serious health threat is defined as a signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health of patients, users or other persons, and that requires prompt remedial action for other patients, users, or other persons.

The requirements for immediate reporting (i.e., no more than 24 hours after learning of the event) are described in 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* (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

The investigator is also responsible for reporting medical device deficiencies (see Section 5.4.4). For a device deficiency with an associated adverse event, this means that the investigator must report both an adverse event and a medical device deficiency (Section 5.4.4).

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.3 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

Guidelines for categorizing adverse events are provided in Appendix 18.

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, but prior to study drug initiation:

- After informed consent has been obtained but prior to the first administration of intravitreal ranibizumab 0.5 mg) for *patients in the* **PDS arm or comparator arm** (either as a supplemental treatment prior to Week 60 or a loading dose at Week 60)

only serious adverse events caused by a protocol-mandated intervention should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

- With the exception that all severe acute respiratory coronavirus 2 (SARS-CoV-2)–related (due to viral infection or vaccine administration) adverse events will be reported for *patients in the* **comparator arm** from randomization until the patient's final study visit.
- With the exception *of patients in the* **comparator arm** patients that discontinue from *the* study early, all adverse events leading to study discontinuation from randomization will be reported up to their early termination visit.

After initiation of study drug:

- After the first administration of intravitreal ranibizumab 0.5 mg for *patients in the* **PDS arm** (at randomization) or *in the* **comparator arm** (either as a supplemental treatment prior to Week 60 or a loading dose at Week 60) all adverse events will be reported until the patient's final study visit.

For patients *in the PDS arm* who terminate study treatment and discontinue from the study prematurely, all adverse events will be reported up to the early termination visit.

For *patients in the* comparator arm *who* discontinue from *the* study early, all adverse events leading to study discontinuation will be reported up to the early termination visit.

For patients who undergo implant explantation, all adverse events will be reported up to 90 (+7) days after explantation.

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

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

Table 8 provides guidance for assessing adverse event severity.

Table 8 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 5.2.3).

5.3.4 Assessment of Causality of Adverse Events Related to *the* Pharmaceutical Product

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" as applicable on Adverse Event eCRF.

Patients with the PDS: The investigator will assess whether there is a potential association with the study *drug (ranibizumab)*.

Patients Receiving Intravitreal Injections: The investigator will assess whether there is a potential association with each of the following "components" of the study intervention:

- The intravitreal injection procedure
- Ranibizumab (study drug)

The following guidance should be taken into consideration (see also Table 9):

- Temporal relationship of event onset to the initiation of study drug (see Table 9) or due to intravitreal injection procedure
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non–treatment-related factors that are known to be associated with the occurrence of the event

Table 9 Causal Attribution Guidance for the Pharmaceutical Product

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

5.3.5 Assessment of Causality of Adverse Events *to* the Medical Device

Adverse events are recorded on the Adverse Event associated eCRFs and reported to the Sponsor in accordance with instructions provided in this Section (Table 10) and in Sections 5.3–5.6.

For each event recorded on the Adverse Event associated eCRFs, the investigator will make an assessment of seriousness (see Section 5.2.3) and causality (only applicable for adverse events) of the following "components" of the study intervention:

- Implant procedure, insertion tool, *initial fill needle,* or implant
- Refill-exchange procedure or refill needle
- Explant procedure or explant tool

Investigators should use their knowledge of the subject, the circumstances surrounding the event, and an evaluation of any potential alternative cause to determine whether an adverse event is considered to be related to the device or device-related procedure. The guidelines provided in Appendix 18 should be used to assess the causality of adverse events.

Table 10 Assessment of Event Relationship to Device or Device-Related Procedure

Relationship	Explanation
Not related [a]	• Event is not a known side effect of the product category the device belongs to, or of similar devices and procedures • Event has no temporal relationship with the use of the investigational device or the procedures • Event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible • Discontinuation of medical device application or the reduction of the level of activation/exposure and reintroduction of its use (or increase of the level of activation/exposure), do not impact the event (when clinically feasible) • Event involves a body site or an organ not expected to be affected by the device or procedure • Event can be attributed to another cause (e.g., an underlying or concurrent illness or clinical condition, an effect of another device, drug, treatment or other risk factors) • Event does not depend on a false result given by the investigational device used for diagnosis, when applicable • Harms to the patient are not clearly due to use error
Possible	• Relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness or clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should be classified as possible.
Probable	• Relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be required
Causal relationship	Event is associated with the investigational device or with procedures beyond reasonable doubt when: • Event is a known side effect of the product category the device belongs to or of similar devices and procedures • Event has a temporal relationship with investigational device use/ application, or procedures • Event involves a body site or organ that: –The investigational device or procedures are applied to –The investigational device or procedures have an effect on • Event follows a known response pattern to the medical device (if the response pattern is previously known) • Discontinuation of medical device application (or reduction of the level of activation or exposure) and reintroduction of its use (or increase of the level of activation or exposure), impacts the seriousness of the event (when clinically feasible and/or relevant) • Other possible causes (e.g., an underlying or concurrent illness or clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out • Harm to the patient is due to use error

[a] Complications of procedures are considered to be not related if said procedures would have also been applied to patients in the absence of investigational device use/application.

5.3.6 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 (trace or greater)

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

  Active inflammation in the vitreous should be clinically differentiated from cellular debris from prior episodes of inflammation, hemorrhage, or other causes.
- Endophthalmitis: diffuse intraocular inflammation predominantly involving the vitreous cavity but possibly also involving the anterior chamber, implying a suspected underlying infectious cause

Vitreous and/or aqueous humor samples should be collected prior to initiating antimicrobial treatment for presumed infectious endophthalmitis and sent for microbiological testing, including culture (see Appendix 16).

5.3.6.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases; record only endophthalmitis that resulted in ≥30 letters loss rather than the decrease of ≥30 letters in BCVA, anterior or posterior chamber cell and flare). 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.

5.3.6.2 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.

5.3.6.3 Persistent or Recurrent Adverse Events

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

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

5.3.6.4 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 × upper limit of normal (ULN) associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

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

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.6.3 for details on recording persistent adverse events).

5.3.6.5 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 5.3.6.3 for details on recording persistent adverse events).

5.3.6.6 Abnormal Liver Function Tests

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

- Treatment-emergent ALT or AST >3×ULN in combination with total bilirubin >2×ULN
- Treatment-emergent ALT or AST >3×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 5.3.6.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.6.7 Deaths

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

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

If the death is attributed to progression of diabetes mellitus, diabetes mellitus progression" should be recorded on the Adverse Event eCRF.

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

5.3.6.8 Preexisting Medical Conditions

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

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When

recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.6.9 Worsening of Diabetic Retinopathy

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

5.3.6.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.3), except as outlined below.

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

- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

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

  The patient has not experienced an adverse event

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

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

5.3.6.11 Cases of Accidental Overdose or Medication Error

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

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

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

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

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

In addition, all special situations associated with ranibizumab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

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

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

5.3.6.12 Patient Preference Questionnaire and Treatment Satisfaction Questionnaire Data

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

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events (defined in 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.4; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)
- Adverse device effects (see Section 5.4.4 for details on reporting requirements)
- Serious adverse device effects, both anticipated and unanticipated (see Section 5.4.4 for details on reporting requirements)
- *Device deficiencies that led to or could have led to a serious adverse event* (see Section 5.4.4)

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

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

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

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

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

Telephone No.: [redacted]

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

Telephone No.: [redacted]

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

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug (the first intravitreal ranibizumab 0.5 mg) for **PDS arm** or prior to randomization for the **comparator arm**, (either as a supplemental treatment prior to Week 60 or a loading dose at Week 60), **only serious adverse events caused by a protocol-mandated intervention should be reported.** With the exception that for **comparator arm** patients that discontinue from study early, all serious adverse events or adverse events of special interest leading to study discontinuation from randomization, will be reported up to their early termination visit.

The paper Clinical Trial Adverse Event/Special *Situations* 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 (intravitreal ranibizumab 0.5 mg) for the **PDS arm** or **comparator arm** (either as a supplemental treatment prior to Week 60 or a loading dose at Week 60) **serious adverse events and adverse events of special interest will be reported until the final study visit.**

For the **PDS arm** patients who terminate from study treatment and study early, all adverse events will be reported up to the early termination visit. For the **comparator arm** patients that discontinue from study early, all serious adverse events or adverse events of special interest leading to study discontinuation will be reported from randomization up to their early termination visit.

Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/Special *Situations* Form provided to investigators should be completed and

submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

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

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within *3 months* after the final intravitreal injection of ranibizumab or 1 year after the final refill-exchange of ranibizumab. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. *If medically necessary, as per investigator's judgement and following discussion with the Medical Monitor, a preservative-free saline flush of implant content may be performed with a refill needle.* Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Congenital Anomalies/Birth Defects and Abortions

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

5.4.4 Reporting Requirements for Medical Devices

The investigator must report all deficiencies associated with medical devices (PDS implant and/or ancillary devices) (defined as inadequacy with respect to labeling, identity, quality, durability, reliability, safety, performance, including malfunctions or use error and their packaging) that could have led to a serious adverse event if suitable action had not been taken, intervention had not occurred, or circumstances had been less fortunate, to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

In this study, the PDS implant, ancillary devices, intravitreal ranibizumab 0.5 mg pre-filled syringe (if applicable), and intravitreal ranibizumab 0.3 mg pre-filled syringe (if applicable) are considered medical devices.

The investigator should follow the guidance outlined in the Device Deficiencies and Study Drug Complaints Manual and provide as much information as possible to the Sponsor, including the product batch number.

If the medical device (PDS implant and/or ancillary devices) and/or associated procedures result in an adverse event to the study patient, the event must be reported on the associated eCRFs and submitted through the EDC system by the investigator. If the event is serious, including serious health threats (see Section 5.2.6), or of special interest, the associated eCRFs must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.4.2. See Section 5.2.2 for definitions of adverse events related to the medical device.

The investigator must report all deficiencies associated with the intravitreal ranibizumab 0.5-mg *and 0.3 mg* single-use containers to the Sponsor (deficiencies defined as inadequacy with respect to labeling, identity, quality, durability, reliability, safety, performance, including malfunctions or use error and their packaging). The investigator should *forward* as much information to the Sponsor immediately (i.e., no more than 24 hours after learning of the event*); the Sponsor will then fill out the IMP Deviation form.*

If the intravitreal ranibizumab 0.5-mg single-use container results in an adverse event to the study patient, the event must be reported on the Adverse Event eCRF and submitted through the EDC system. If the event is serious, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.4.2.

To report a device deficiency, the investigator should follow the guidance outlined in the Device Deficiencies and Study Drug Complaints Manual and provide as much information as possible to the Sponsor, including device lot number.

If a medical device results in an adverse event to an individual other than the study patient (e.g., study site personnel), the event should be reported to the Sponsor (refer to the Device Deficiencies and Study Drug Complaints Manual for further details).

For further information on returning the PDS implant and ancillary devices associated with a complaint, see the Device Deficiencies and Study Drug Complaints Manual.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as the final study visit for patients who complete study treatment; for patients who discontinue study treatment early but continue to participate in the study, the adverse events reporting period is until their last or final study visit), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special *Situations* Form using the fax number or email address provided to investigators.

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

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

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed below:

Drug *or* Device	Document
PDS	PDS Investigator's Brochure
Intravitreal ranibizumab 0.5 mg	PDS Investigator's Brochure
Intravitreal ranibizumab 0.3 mg	*Lucentis® (ranibizumab for injection)* U.S. Prescribing Information

PDS =Port Delivery System with ranibizumab.

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The primary analysis will be performed when all patients have completed the Week 52 visit or have discontinued from the study prior to Week 52, all data collected through Week 52 are in the database, and the data have been cleaned and verified.

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

The final analysis will be performed when all patients have either completed the study period (at the Sponsor's discretion, depending on health authority approval of the PDS for the DR indication and Sponsor decision) or discontinued early from the study, all data from the study are in the database, and the database is locked.

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

Descriptive summaries will include the mean, standard deviation, median, and range for continuous variables, and counts and percentages for categorical variables. Detailed specifications of the statistical methods will be described in the Statistical Analysis Plan (SAP).

6.1 DETERMINATION OF SAMPLE SIZE

Patients will be randomly allocated in a 5:3 ratio to the PDS arm or the comparator arm.

The primary endpoint is the proportion of patients with a ≥2-step improvement from baseline on the ETDRS-DRSS at Week 52. A sample size of 160 patients will provide over 99% power to demonstrate an at least 35% absolute improvement in proportion of patients with a ≥2-step improvement on ETDRS-DRSS at Week 52 under the following assumptions:

- An achievement of a ≥2-step improvement on the ETDRS-DRSS at Week 52 in 15% of patients in the comparator arm (Eylea® U.S. Package Insert) *(Brown et al. 2021)*
- Fisher's exact test
- A 4.96% two-sided type I error rate (after adjustment for planned interim data reviews conducted by the iDMC prior to analysis of the primary efficacy endpoint; see Section 3.1.6)
- A 15% dropout rate by Week 52

In case the 15% dropout rate by Week 52 is deemed under-estimated during the study enrollment period, the sample size may be increased accordingly based on a revised dropout rate estimate.

6.2 SUMMARIES OF CONDUCT OF STUDY

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

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics such as age, sex, race, and disease characteristics (duration of diabetes, type of diabetes, DRSS, BCVA, CST, etc.) will be summarized by treatment group using descriptive statistics.

Exposure to study treatment after randomization (number of study treatments: loading doses, initial fill/refill-exchange) and duration of treatment will be summarized.

6.4 EFFICACY ANALYSES

Efficacy analyses will be based on the *ITT* population comprising all patients who are randomized, with patients grouped according to the treatment *assigned at randomization*.

Unless otherwise noted, analyses of efficacy outcome measures will be stratified by the randomization stratification factors (ETDRS-DRSS level [47 vs. 53] and intraretinal or subretinal fluid status on SD-OCT [present vs. absent] as assessed at baseline by a central reading center) as recorded in IxRS.

A nominal type I error penalty of 0.0001 (two-sided) will be taken for each time the iDMC reviews unmasked data prior to the primary analysis. At the time of the primary analysis, it is estimated that four interim data reviews will have been conducted by the iDMC; therefore, efficacy analyses will be performed at a significance level of 0.0496. The actual adjustment will depend on the actual number of iDMC reviews.

In addition to p-values for statistical tests, the estimates and CIs will be provided for the mean (for continuous variables) or proportion (for binary variables) for each treatment group and the difference in means or proportions between two treatment groups. All CIs will be two sided and at the 95.04% level.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients with a ≥2-step improvement from baseline on the ETDRS-DRSS at Week 52.

The primary estimand is defined as follows:

- Population: *a*dult patients with moderately severe or severe NPDR (ETDRS-DRSS level 47 or 53) and no presence of CI-DME
- Variable: *p*roportion of patients with a ≥2-step improvement from baseline on the ETDRS-DRSS at Week 52
- Intercurrent events *that occur prior to Week 52:*

a) *For patients who receive any supplemental treatment: a composite variable strategy will be applied. Patients with this intercurrent event will be regarded as nonresponders (i.e., they are regarded as not achieving a 2-step improvement on the EDTRS-DRSS).*

b) *For patients who receive any* prohibited *therapy* (as defined in Section 4.4.2) *or* PRP*: a composite variable strategy will be applied in which patients with this intercurrent event will be regarded as non-responders.*

c) *For patients who discontinue* study treatment (PDS arm) or discontinue *from the* study (comparator arm) due to an adverse event*: a treatment policy strategy will be applied where all observed values will be used regardless of the occurrence of the intercurrent event.*

d) *For patients who discontinuestudy* treatment (PDS arm) or discontinue study (comparator arm) due to lack of efficacy per investigator's judgment*: a treatment policy strategy will be applied in which all observed values will be used regardless of the occurrence of the intercurrent event.*

- Population-level summary: *d*ifference in proportion between PDS and comparator arms as *assigned at randomization*

The primary analysis will be performed using the Cochran–Mantel–Haenszel test (CMH) stratified by baseline ETDRS-DRSS level (47 vs. 53) and intraretinal or subretinal fluid status on SD-OCT (present vs. absent) as assessed at baseline by a central reading center *and as recorded in IxRS.* If patients receive supplemental treatments, prohibited

treatments, or PRP prior to Week 52 (intercurrent events a–b), they may experience an improvement in the ETDRS-DRSS level as a result which would potentially bias the results in favor of an ineffective treatment. Their ETDRS-DRSS level at Week 52 will be imputed using the assumption that they did not have a ≥2-step improvement from baseline. For patients who discontinue study treatment (PDS arm) or discontinue from the study (comparator arm) due to adverse events or lack of efficacy (per the investigator's assessment), their assessments after study treatment or study discontinuation (but before receiving supplemental treatment or prohibited treatment or PRP) will be included in the analyses. Other missing ETDRS-DRSS levels at Week 52 will be imputed using the last observed DRSS levels prior to Week 52. Patients with missing baseline ETDRS-DRSS level will be excluded from the analysis.

The proportion of patients in each treatment arm and the overall difference in proportions between treatment arms will be estimated using the weighted average of the observed proportions and the differences in observed proportions over the strata defined by randomization stratification factors of baseline ETDRS-DRSS and baseline intraretinal or subretinal fluid status using the CMH weights (Cochran 1954; Mantel and Haenszel 1959). CIs of the difference in proportions between treatment arms will be calculated using the normal approximation to the weighted proportions (Mehrotra and Railkar 2000).

Supplementary Analyses for the Primary Endpoint

A supplementary analysis will be performed in which patients experiencing any intercurrent event prior to Week 52 will be regarded as a non- responder (i.e., they are regarded as not achieving a 2-step improvement on the EDTRS-DRSS). The analysis method and the missing data handling rule for this supplementary analysis will be the same as those for the main analysis.

In order to estimate the treatment effect in the absence of the COVID-19 pandemic, a supplementary analysis will be performed using the same elements of the estimand as those in the main analysis but including additional intercurrent events related to COVID-19. For these COVID-19-related intercurrent events (as detailed in the SAP), the hypothetical strategy of censoring observations after the intercurrent event will be used. Missing data will then be imputed using the last observed outcome prior to the intercurrent event. The analysis methods for this supplementary analysis will be the same as those for the main analysis.

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

6.4.2 Secondary Efficacy Endpoints

The key secondary endpoints are as follows:

1. Rate of patients developing a vision-threatening complication (defined as PDR or ASNV) or CI-DME (defined as CST ≥325 μm) through Week 52
2. Rate of patients developing PDR or ASNV through Week 52

3. Rate of patients developing CI-DME (defined as CST ≥325 µm) through Week 52
4. Rate of patients developing ≥2-step worsening from baseline on the ETDRS-DRSS through Week 52
5. Proportion of patients with ≥3-step improvement from baseline on the ETDRS-DRSS at Week 52
6. *Rate* of patients *developing* ≥3-step worsening from baseline on the ETDRS-DRSS *through* Week 52

A fixed sequence testing procedure (Westfall and Krishen 2001) will be used to control the overall type I error for the primary and the key secondary endpoints. If the primary endpoint is positive, then the first key secondary endpoint will be tested. The same rule will follow for testing the rest of the key secondary endpoints as the order shown above.

The rate of patients developing vision-threatening complications through Week 52, the rate of patients developing PDR or ASNV through Week 52, the rate of patients developing CI-DME through Week 52, the rate of patients developing a ≥2-step worsening in DR severity from baseline through Week 52 and the rate of patients developing a ≥3-step worsening in DR severity from baseline through Week 52 will be estimated using the Kaplan-Meier method based on time to the first such event occurs. The estimand for these endpoints will be as follows:

- Population: Adult patients with moderately severe or severe NPDR (ETDRS-DRSS level 47 or 53) and no presence of CI-DME
- Variable: same as the endpoint
- Intercurrent events *that occur* prior to Week 52
  - *For patients who receive any supplemental treatment: a composite variable strategy will be applied where the intercurrent event is considered to be an event in the analysis.*
  - *For patients who receive any prohibited therapy or PRP: a composite variable strategy will be applied where the intercurrent event is considered to be an event in the analysis.*
  - *For patients who discontinue* study treatment (PDS arm) or discontinue study (comparator arm) due to an adverse event: *a treatment policy strategy will be applied where all observed values will be used regardless of the occurrence of the intercurrent event.*
  - *For patients who discontinue* study treatment (PDS arm) or discontinue study (comparator arm) due to lack of efficacy per investigator's judgment: *a treatment policy strategy will be applied where all observed values will be used regardless of the occurrence of the intercurrent event.*
- Population-level summary: Difference in event rate between PDS and comparator arms grouped as *assigned at randomization* and hazard ratio

Patients who do not have the endpoint event will be censored at the last assessment visit at or before Week 52. The difference in event rates between the two treatment groups will be compared using the log-rank test stratified by the randomization stratification factors. In addition, the ratio of the hazard rates between the two treatment groups (hazard ratio) will be estimated using the Cox proportional hazard models, stratified by the randomization stratification factors.

The estimand and analysis method for the proportion of patients with ≥3-step improvement from baseline on the ETDRS-DRSS at Week 52 will follow those for the primary endpoint.

Additional secondary endpoints are listed in Section 2.1.2. The binary secondary endpoints will be summarized using descriptive statistics based on all observed data. The binary endpoints measured during the comparator-controlled treatment phase (i.e., the first 52 weeks of the study) will also be analyzed with estimand, analysis method, and data handling rules following those for the primary endpoint.

The time-to-event endpoints will be summarized using the Kaplan-Meier method. Patients who do not have the endpoint event will be censored at the last assessment visit.

The continuous secondary endpoints will be summarized using descriptive statistics based on all observed data. The continuous endpoints measured during the controlled treatment phase will also be analyzed using the mixed-effect model for repeated measures (MMRM).

The *estimand* for the continuous secondary endpoints *will be as follows:*

- *Population: Adult patients with moderately severe or severe NPDR (ETDRS-DRSS level 47 or 53) and no presence of CI-DME who are naïve to any treatment for DR in the study eye*
- *Variable: same as the endpoint*
- *Intercurrent events that occur prior to Week 52:*
  - *For patients who receiveany supplemental treatment: a treatment policy strategy will be applied where all observed values will be used regardless of the occurrence of the intercurrent event.*
  - *For patients who receive any prohibited therapy or PRP: a treatment policy strategy will be applied where all observed values will be used regardless of the occurrence of the intercurrent event.*
  - *For patients who discontinue study treatment (PDS arm) or discontinue study (comparator arm) due to an adverse event: a treatment policy strategy will be applied where all observed values will be used regardless of the occurrence of the intercurrent event.*

- *For patients who discontinuestudy treatment (PDS arm) or discontinue study (comparator arm) due to lack of efficacy per investigator's judgment: a treatment policy strategy will be applied where all observed values will be used regardless of the occurrence of the intercurrent event.*

- *Population-level summary: Difference in adjusted mean between PDS and comparator arms grouped as assigned at randomization*

The dependent variable in the MMRM model is the change from baseline at post-baseline visits and the independent variables are the treatment group, time, treatment-by-time interaction, baseline score (continuous), and the randomization stratification factors of baseline ETDRS-DRSS level (47 vs. 53) and baseline intraretinal or subretinal fluid status (present vs. absent) as fixed effects. The MMRM model will assume an unstructured covariance structure. If there are convergence problems with the model, then a compound symmetry covariance or an AR (1) covariance structure will be used.

6.4.2.1 Supplementary Analysis for the Key Time-to-Event Secondary Endpoints

A supplementary analysis will be performed where *all* intercurrent events from the *key secondary endpoints with time-to-event outcomes* (see Section 6.4.1) are treated as events.

The estimand is defined as follows:

- Population: Adult patients with moderately severe or severe NPDR (ETDRS-DRSS level 47 or 53) and no presence of CI-DME
- Variable: Same as the endpoint
- *Intercurrent events that occur prior to Week 52: a composite variable strategy will be applied to following intercurrent events:* receipt of supplemental intravitreal ranibizumab 0.5 mg injection *treatments*, prohibited *therapies, PRP,* or *discontinued from the study or treatment due to lack of efficacy or adverse event prior to Week 52, for which these intercurrent events will be treated* as events in the analysis.
- Population-level summary: Difference in event rate between PDS and comparator arms grouped as *assigned at randomization* and hazard ratio

At the primary analysis, the hypothesis testing will be conducted for endpoints through Week 52 only. Additional details regarding the plan for the secondary endpoint analyses will be provided in the SAP.

6.4.3 Exploratory Efficacy Endpoints

Details regarding the analysis of the exploratory efficacy endpoints will be provided in the SAP.

6.5 SAFETY ANALYSES

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

Safety data will be summarized for the following two populations:

- The safety-*evaluable* population during the comparator-controlled treatment period, comprising all patients who receive study treatment (PDS or comparator) after randomization through Week 52 with patients grouped according to treatment actually received. Patients who receive *the* PDS implant before Week 52 will be included in the PDS treatment arm, otherwise patients will be included in the comparator arm.

  The safety assessment will be based on data collected on and after initiation of study treatment for patients in the PDS arm. For the comparator arm, only key safety events will be collected during the first 60 weeks (serious adverse events *caused by a protocol-mandated intervention*, SARS-CoV-2-related adverse events, and adverse events leading to discontinuation, see Section 5.3.1) or until initiation of study treatment, whichever comes first.
- The PDS safety population, comprising all patients who receive the PDS implant, including patients in the comparator arm who cross over to receive PDS at Week 64.

  The safety assessment will be based on data observed during and after *the first loading dose (prior to insertion of the* PDS implant).

At the time of the primary analysis, safety data will mainly be summarized based on the complete Week 52 data by treatment group in the safety-*evaluable* population during the comparator-controlled treatment period. Safety data will also be summarized for the PDS safety population at the primary analysis and at the final analysis.

6.5.1 Adverse Events

All verbatim adverse event terms will be mapped to MedDRA thesaurus terms, and adverse event severity will be graded according to the Adverse Event Severity Grading Scale (see Table 8).

Adverse events will be tabulated by body system and preferred term. All adverse events, serious adverse events, deaths, adverse events leading to discontinuation of study treatment, adverse events of special interest, and adverse events judged to be related to study treatment or procedure will be summarized as described above. In addition, adverse events of special interest, and ocular adverse events of special interest will be summarized by the adverse event onset day (≤37 days vs. >37 days post-implant insertion). These summaries comprise all adverse events reported in the safety populations, regardless of causality. Separate summaries will be prepared for ocular

and non-ocular adverse events, with events in the study eye and fellow eye summarized separately.

All adverse device effects, serious adverse device effects (anticipated and unanticipated) and adverse device effects leading to discontinuation of study treatment will be summarized as described above. These summaries comprise the subset of adverse events in which causality is suspected to be related to the device and/or procedure.

Adverse device effects reported to be related to the use of the investigational medical devices by users or other persons who have been exposed to the medical device but are not the study subject will be summarized separately from the safety data reported for the safety populations.

6.5.2 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, slitlamp examination, and indirect ophthalmoscopy. Changes from baseline for selected ocular assessments will be tabulated. The presence of intraocular inflammation and vitreous hemorrhage, as determined on slitlamp examination, will be tabulated by grade (according to grading scales for flares and cells and vitreous hemorrhage density and functional grading in Appendix 8 and Appendix 9, respectively). The presence of retinal break or detachment as determined from ophthalmoscopy will be tabulated.

Additional details regarding the safety analysis plan will be provided in the SAP.

6.6 PHARMACOKINETIC ANALYSES

The PK analysis will include patients who receive study treatment and have sufficient data to enable estimation of key parameters, with patients grouped by study arm. Individual and mean serum ranibizumab concentration-versus-time data will be tabulated and plotted by study arm for all patients. Sensitivity analysis may be performed with the population that excludes patients who receive fellow eye treatment and/or patients who receive supplemental treatment.

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

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis will include all patients with at least one ADA assessment. For estimation of the baseline prevalence, patients in the PDS arm who do not receive study treatment will also be included in the summary as PDS patients.

The numbers and proportions of ADA-positive patients and ADA-negative patients prior to study treatment (prevalence) and after study treatment administration (incidence) will be summarized. Details for the ADA analyses *and neutralizing antibodies* will be provided in the SAP.

The relationship between ADA status *and neutralizing antibodies* and safety, efficacy, PK, and biomarker endpoints may be analyzed and reported via descriptive statistics.

6.8 BIOMARKER ANALYSES

Although no formal statistical analysis of exploratory biomarkers will be performed, data may be analyzed in the context of this study and in aggregate with data from other studies.

The PD biomarker analysis will include patients who receive study treatment and have sufficient data to enable assessment of potential changes in biomarkers in response to treatment during the conduct of this study. PD biomarker analyses will be focused primarily on, but not limited to, the change in free VEGF or other angiogenesis-related biomarker concentrations (absolute or percent change as appropriate) over time. The data will be analyzed in the context of ranibizumab pharmacokinetics, using a longitudinal model approach, to gain an understanding of the relationship between ranibizumab concentrations and target modulation. Results will be reported in a separate document from the Clinical Study Report.

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

6.9 PATIENT TREATMENT EXPERIENCE ANALYSES

Details regarding analysis of the patient treatment experience endpoints will be provided in the SAP.

6.10 INTERIM ANALYSIS

Interim safety analyses will be performed by the iDCC periodically (approximately every 6 months) and will be reviewed by the iDMC. Interim efficacy or futility analyses are not planned.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and central reading center reports and images 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.

Patient-reported outcome (PRO) data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, *images*, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from

automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

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

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

Starting from the implementation of the protocol version 2, the study will also meet the safety reporting requirements of ISO 14155:2020 and the E.U. MDR 2017/745.

8.2 INFORMED CONSENT

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

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

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

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

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

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

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

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

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

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

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will has implemented a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor has identified potential risks associated with critical trial processes and data and has implemented plans for evaluating and controlling these risks. Risk evaluation and control included the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

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

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor and/or its designee will perform study management, oversight of data management,

statistical programming, project management, monitoring, vendor management, and data management (quality checking of data).

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

Approximately 90 sites will participate to enroll approximately 160 patients. An IxRS will be used for patient enrollment and for management of study drug/device requests and shipments.

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

Data will be recorded via an EDC system using eCRFs (see Section 7.1).

An iDMC will be employed to monitor and evaluate patient safety throughout the study (see Section 3.1.6).

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be provided upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

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

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect

proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

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

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

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

9.7 PROTOCOL AMENDMENTS

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

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

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Appendix 1
Schedule of Activities: Screening

	Screening (–21 Days to Randomization)
Informed consent	x
Review of inclusion and exclusion criteria	x
Medical and surgical history	x
Demographic data	x
Contact IxRS	x
Vital signs [a]	x
Concomitant medications [b]	x
Adverse events [c]	x
Concurrent ocular procedures [d]	x
Pregnancy test [e]	x
Urinalysis [f]	x
Hematology [f]	x
Chemistry [f]	x
Coagulation [f]	x
HbA_{1c} [g]	x
Best-corrected visual acuity	x
Intraocular pressure [h]	x
Slitlamp examination	x
Dilated binocular indirect ophthalmoscopy	x
SD-OCT [i]	x
Color fundus photography [i]	x
Fluorescein angiography [i]	x
Lens photo (fundus reflex photograph) [i]	x
OCT-A (at selected sites) [i]	x

HbA_{1c} = glycosylated hemoglobin; IxRS = interactive voice or web-based response system; *PDS = Port Delivery System with ranibizumab;* OCT-A = optical coherence tomography–angiography; SD-OCT = spectral-domain optical coherence tomography.

Note: All ocular assessments are to be performed for both eyes unless noted otherwise.

[a] Vital signs consist of blood pressure and pulse measurement while patient is in a seated position after resting for 5 minutes. Height and weight measurement will be recorded at screening visit only.

[b] Record any concomitant medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) including pre- and post-treatment antimicrobial and anti-inflammatory medications used by the patient within 7 days prior to initiation of study treatment (intravitreal ranibizumab 0.5 mg) if in the PDS arm or all medications used by the patient within 7 days prior to the randomization/Day 1 study visit (comparator arm). Protocol-specified procedural medications administered at the site will not be recorded (e.g., dilating drops; fluorescein dyes; implant insertion, refill-exchange, and explantation procedural medications).

[c] After informed consent has been obtained but prior to initiation of study drug (intravitreal ranibizumab 0.5 mg) only serious adverse events caused by a protocol-mandated intervention should be reported. Adverse events assessed by the qualified ophthalmologist as related to implant insertion, refill-exchange, and explantation- should be followed until the event resolves or the event is assessed as irreversible, chronic, or stable, even if the patient's participation in the study is over.

[d] 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.

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

[f] Obtain prior to fluorescein angiography. Hematology includes hemoglobin. Chemistry includes glucose, HbA_{1c} (see footnote "g"), creatinine, total and direct bilirubin, total protein, AST, and ALT. Urinalysis includes protein, ketones, glucose, bilirubin, and urobilinogen.

[g] Results obtained for HbA1c up to 2 months prior to screening are acceptable. *HbA1c may be retested within the 21-day screening period using the most recent results for determination of patient eligibility.*

[h] 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.

[i] Refer to central reading center manual for details.

Appendix 2
Schedule of Activities: PDS Arm

Table 1 PDS Arm: Randomization to Week 52

Week	R (Day 1)	Pre-I [a] 4	Delayed Pre-I [a] 8	Implant [a]	PI-V1	PI-V2	8 [a]	12	16	20	24	28	32	36	40	44	48	52
Visit window (days)	–21 days from Scr	±7	±7	1–14 days from last LD		±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Review of inclusion and exclusion criteria	x																	
Contact IxRS	x	x	x	x											x			
Concomitant medications [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events, *adverse device effects and device deficiencies* [c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures [d]	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x
RetTSQs [e]	x																	x
PPPQ [e]																		x
Pregnancy test [f]	x	x	x												x			
HbA_{1c} [g, h]	x						x					x			x			x
Serum PK sample [g, h]	x	(x) [i]	x				x	(x) [j]				x			x			x
Serum ADA sample [g, h]	x	(x) [i]	x				x	(x) [j]				x			x			x
Aqueous humor sample (optional) [g, h, k, l, m]	x	(x) [i]	x									x			x			
Plasma sample (if aqueous humor sample collected) (optional) [g, h, m]	x	(x) [i]	x									x			x			
Blood sample for genotyping (optional) [g, n]	x																	
Best-corrected visual acuity	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Intraocular pressure [o]	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Slitlamp examination	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 2: Schedule of Activities: PDS Arm cont.

Week	R (Day 1)	Pre-I [a] 4	Delayed Pre-I [a] 8	Implant [a]	PI-V1	PI-V2	8 [a]	12	16	20	24	28	32	36	40	44	48	52
Visit window (days)	−21 days from Scr	±7	±7	1–14 days from last LD		±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Dilated binocular indirect ophthalmoscopy [p]	x	x	x	x [q]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Post-refill-exchange dilated binocular indirect ophthalmoscopy [p]															*x*			
SD-OCT [r]		x	x				x	x	x	x	x	x	x	x	x	x	x	x
Fundus photography [r]		(x) [s]	x						x			x			x			x
Fluorescein angiography [r]		(x) [s]	x									x						x
Lens photo (fundus reflex photograph) [r]																		x
Implant photographs [r, t]					x	x	x	x	x	x		x		x		x		x
OCT-A (at selected sites) [r, u]		x	x				x	x	x	x	x	x	x	x	x	x	x	x
AS-OCT (at selected sites) [r, u]											*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Pre- and post-study-treatment antimicrobials [v]				x											x			
Intravitreal ranibizumab 0.5-mg injection (loading doses)	x	x	x															
Ranibizumab-filled implant insertion [w]				x														
Implant insertion, refill-exchange, explantation- video [x]				x											x			
Implant insertion evaluation [y]				x														
Refill-exchange [z]															x			
Supplemental intravitreal ranibizumab 0.5 mg (if supplemental treatment criteria are met) [aa]							x	x	x	x	x	x	x	x		x	x	x

Appendix 2: Schedule of Activities: PDS Arm cont.

Week	R (Day 1)	Pre-I [a] 4	Delayed Pre-I [a] 8	Implant [a]	PI-V1	PI-V2	8 [a]	12	16	20	24	28	32	36	40	44	48	52
Visit window (days)	−21 days from Scr	±7	±7	1–14 days from last LD		±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Post-treatment finger-counting test [bb]	x	x	x												x			
Follow-up call [cc]	x	x	x												x			

ADA = anti-drug antibody; BCVA = best-corrected visual acuity; *EDC = electronic capture system;* HbA_{1c} = glycosylated hemoglobin; IxRS = interactive voice or web-based response system; LD = loading dose; OCT-A = optical coherence tomography-angiography; PDS = Port Delivery System with ranibizumab; PI-V1 = post-implant insertion Visit 1 (1 day after implant insertion); PI-V2 = post-implant insertion Visit 2 (7 [±2] days after implant insertion); PK = pharmacokinetic; PPPQ = PDS Patient Preference Questionnaire; Pre-I = pre-implant; R = randomization; RetTSQs = Retinopathy Treatment Satisfaction Questionnaire, status version; Scr = screening; SD-OCT = spectral-domain optical coherence tomography; (x) = conditional/optional (refer to footnote).

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, unless noted otherwise. Dark gray shaded columns indicate implant and refill-exchange visits. Light gray *indicates* Week 8 Delayed Pre-Implant visit.

[a] PDS implant insertion may be delayed due to extenuating circumstances *following consultation* with *the* Medical Monitor. If implant insertion surgery is delayed from Week 4 to Week 8, perform assessments as outlined in the delayed pre-implant visit (Delayed Pre-I) Week 8 column, then perform implant, PI-V1, PI-V2, and subsequent Q4W study visits starting at Week 12 study visit and follow the *schedule of activitities* as outlined in this appendix until the end of the study. The implant insertion visit must occur within the Week 4 window and 1–14 days from last LD or within the Week 8 window if surgery is delayed to Week 8 and 1–14 days from last LD.

[b] Record any concomitant medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) including pre- and post-treatment antimicrobial and anti-inflammatory medications used by the patient within 7 days prior to initiation of study treatment (intravitreal ranibizumab 0.5 mg if in PDS arm) or all medications used by the patient within 7 days prior to the randomization/Day 1 study visit (comparator arm). Protocol-specified procedural medications administered at the site will not be recorded (e.g., dilating drops; fluorescein dyes; implant insertion, refill-exchange, and explantation procedural medications).

[c] Adverse events will be recorded starting immediately after initiation of study drug (intravitreal ranibizumab 0.5 mg for PDS arm) through the last study visit. *Device deficiencies will be recorded in the EDC after implementation of protocol Version 2. Adverse events and device deficiencies causality will be evaluated by the qualified ophthalmologist.* Adverse events assessed by the qualified ophthalmologist as related to implant insertion, refill-exchange, and explantation should be followed until the event resolves or the event is assessed as irreversible, chronic, or stable, even if the patient's participation in the study is over.

[d] 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.

[e] Must be interviewer-administered by site personnel (other than BCVA examiner) prior to any other study procedures. *In extenuating circumstances, may be administered by phone interview prior to in-office study visit.*

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

[g] Obtain prior to fluorescein angiography.

[h] Collect prior to intravitreal ranibizumab injection, if applicable.

[i] If implant insertion surgery is delayed to Week 8, do not collect PK, ADA, aqueous humor (optional), or plasma (optional) samples at the Week 4 visit.

[j] If implant insertion surgery is delayed to Week 8, collect PK and ADA samples at the Week 12 visit.

[k] For the PDS arm a maximum of four aqueous humor samples may be collected per refill interval (defined as the period beginning at either implantation or device refill-exchange procedure and ending at the visit prior to the next subsequent scheduled refill-exchange, i.e., implant insertion to Week 36; Week 40 to Week 72, etc.) either from an aqueous humor sample collection outlined here in Appendix 2 or in Appendix 6.

[l] To allow for IOP renormalization, collect aqueous humor sample at ≥45 minutes prior to the refill-exchange procedure. However, the refill-exchange procedure may be performed <45 minutes following aqueous humor sample collection if IOP has normalized. Alternatively, sample may be collected immediately after refill-exchange procedure at the investigator's discretion.

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

[n] Collect at randomization or at any time during the study.

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

[p] Dilated ophthalmoscopy examinations will also be performed in the study eye 1 day and 7 (±2) days after implant (post-implant Visits 1 and 2, respectively); afterward, perform dilated ophthalmoscopy examinations at each visit *as well as before and after refill-exchange* to monitor the implant placement and to evaluate other implant problems.

[q] Performed in operating room. Upon completion of the PDS implant insertion surgery, patients will have dilated indirect ophthalmoscopy performed to monitor the implant placement and to evaluate any potential implant problems. (The recording of indirect ophthalmoscopy results using electronic data capture is not required at the implant visit.)

[r] Refer to central reading center manual for details.

[s] If implant insertion surgery is delayed to Week 8, do not collect color fundus photograph and FA at the Week 4 visit.

[t] In addition to the timepoints listed, implant photographs should be taken at any visit if there are concerns with implant function. *Implant photographs may be captured before and after application of topical fluorescein to the surface of the eye over the implant to monitor conjunctiva (e.g., if suspected conjunctival erosion). Implant photos should* be taken only after PDS has been implanted.

[u] Only at selected study sites. Perform pre-treatment. *If a site has the imaging capability to perform AS-OCT angiography (AS-OCT-A), then the site can perform this optional assessment.*

[v] The use of self-administered antimicrobial ophthalmic drops is required before and after PDS implant insertion. The use of self-administered antimicrobial ophthalmic drops prior to refill-exchange is optional per the investigator's discretion but is required after refill-exchange. The use of anti-inflammatory ophthalmic drops is required after implant insertion and explantation. Dosing per standard of care.

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

[x] At sites that permit video recording. The implant insertion, explantation, refill-exchange, and any other ocular surgical procedures (e.g., conjunctival erosion or retinal detachment repair) performed in the study eye will be captured on video unless the study center has policies in place that prohibit these procedures from being video captured.

[y] Upon completion of the implant insertion surgery, complete the implant insertion evaluation electronic Case Report Form to indicate surgical details of the insertion procedure.

[z] *Perform implant refill-exchange procedure with IxRS-assigned kit of ranibizumab 100 mg/mL. If a refill-exchange procedure needs to be re-attempted prior to the next scheduled visit, pregnancy test for women of childbearing potential, BCVA, IOP measurement, slit-lamp exam, dilated binocular indirect ophthalmoscopy, pre- and post-study treatment microbials, and post treatment finger counting test should be repeated at the unscheduled visit. Additional non-invasive ocular assessments in either eye may be performed at the investigator's discretion, including implant images. Note: Visually check implant prior to performing refill-exchange.*

[aa] Patients with the PDS are eligible for supplemental intravitreal ranibizumab 0.5 mg if supplemental treatment criteria are met (see Section 4.3.2.3); if so, the assessments in Appendix 6 must be performed in addition to those listed here. Following supplemental intravitreal ranibizumab 0.5 mg, patients will continue with refill-exchange procedures per protocol. If a patient meets the supplemental treatment criteria within the first 3 months after implant insertion, the investigator must contact the Medical Monitor prior to administering supplemental intravitreal ranibizumab 0.5 mg.

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

[cc] 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.

Table 2 PDS Arm: Week 56 to Final Visit, Early Termination Visit, or Explantation Visits

Week	56	60	64	68	72	76	80	84	88	100	112	Visit X (12W post refill-XCH)	Visit Y (24W post refill-XCH)	Visit Z (36W post refill-XCH)	Optional Visit [a]	Final Visit	Early Term.	Explant Visit
Visit window (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	NA	NA	30 or 90 [b]	NA
Contact IxRS						x					x			x	x	x	x	x
Vital signs																x	x	x
Concomitant medications [c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events, *adverse device effects, and device deficiencies* [d]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures [e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
RetTSQs [f]										x							x	
PPPQ [f]										x							x	
Pregnancy test [g]						x					x			x		x	x	
HbA_{1c} [i]			x			x				x				x		x	x	
Serum PK sample [h, i]			x			x				x							x	x
Serum ADA sample [h, i]			x			x				x							x	x
Aqueous humor sample (optional) [h, j, k, i]				x	x	x				x	x		x	x				
Plasma sample (if aqueous humor sample collected) (optional) [h, i, j]				x	x	x				x	x		x	x				
Aqueous humor sample for biomarkers and ranibizumab concentration (mandatory)																	x [i]	x [i]
Plasma samples for biomarkers (mandatory)																	x [i]	x
Best-corrected visual acuity	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Intraocular pressure [m]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Slitlamp examination	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	

Appendix 2: Schedule of Activities: PDS Arm cont.

Week	56	60	64	68	72	76	80	84	88	100	112	Visit X (12W post refill-XCH)	Visit Y (24W post refill-XCH)	Visit Z (36W post refill-XCH)	Optional Visit [a]	Final Visit	Early Term.	Explant Visit
Visit window (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	NA	NA	30 or 90 [b]	NA
Dilated binocular indirect ophthalmoscopy [n]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Post-refill-exchange dilated binocular indirect ophthalmoscopy [n]						*x*					*x*			*x*				
SD-OCT [o]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Fundus photography [o]			x			x			x	x	x	x	x	x		x	x	
Fluorescein angiography [o]										x				x		x	x	
Lens photo (fundus reflex photograph) [o]										x				x		x	x	
Implant photographs [o, p]		x		x		x		x	x	x	x	x	x	x		x	x	
OCT-A, (at selected sites) [o, q]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	
AS-OCT (at selected sites) [o, q, s]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Pre- and post-study-treatment antimicrobials [r]						x					x			x				
Implant insertion, refill-exchange, explantation video [s]						x					x			x				x
Refill-exchange [t]						x					x			x				
Post-treatment finger-counting test [u]						x					x			x				
Supplemental intravitreal ranibizumab 0.5 mg (if supplemental treatment criteria are met) [v]	x	x	x	x	x		x	x	x	x		x	x		x			
Follow-up call [w]						x					x			x				

Appendix 2: Schedule of Activities: PDS Arm cont.

ADA = anti-drug antibody; BCVA = best-corrected visual acuity; *EDC = electronic capture system;* Explant = explantation; HbA_{1c} = glycosylated hemoglobin; IOP = intraocular pressure; IxRS = interactive voice or web-based response system; LD = loading dose; NA = not applicable; OCT-A = optical coherence tomography–angiography; PDS = Port Delivery System with ranibizumab; PK = pharmacokinetic; PPPQ = PDS Patient Preference Questionnaire; RetTSQs = Retinopathy Treatment Satisfaction Questionnaire, status version; SD-OCT = spectral-domain optical coherence tomography; Term = termination; XCH = exchange.

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, unless noted otherwise. Shaded columns indicate refill-exchange visits.

[a] Perform listed assessments for optional visits after Week 88 only. For unscheduled safety assessment visits prior to Week 76, perform listed assessments in Appendix 5.

[b] Visit window of 30 (+7) days from last completed study visit or 90 (+7) days post-implant insertion (see Section 4.6.2).

[c] Record any concomitant medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) including pre- and post-treatment antimicrobial and anti-inflammatory medications used by the patient within 7 days prior to initiation of study treatment (intravitreal ranibizumab 0.5 mg) for the PDS arm or all medications used by the patient within 7 days prior to the randomization/Day 1 study visit (comparator arm). Protocol-specified procedural medications administered at the site will not be recorded (e.g., dilating drops; fluorescein dyes; implant insertion, refill-exchange, and explantation- procedural medications).

[d] Adverse events will be recorded starting immediately after initiation of study drug (intravitreal ranibizumab 0.5 mg for PDS arm) through the final study visit. *Device deficiencies will be recorded in the EDC from implementation of protocol, Version 2. Adverse events and device deficiencies causality will be evaluated by a qualified ophthalmologist.* Adverse events assessed by the qualified ophthalmologist as related to implant insertion, refill-exchange, and explantation should be followed until the event resolves or the event is assessed as irreversible, chronic, or stable, even if the patient's participation in the study is over.

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

[f] Must be interviewer-administered by site personnel (other than BCVA examiner) prior to any other study procedures. *In extenuating circumstances, the PPPQ may be performed by phone interview prior to an in-office study visit.*

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

[h] To allow for IOP renormalization, collect aqueous humor sample at ≥45 minutes prior to the refill-exchange procedure. However, the refill-exchange procedure may be performed <45 minutes following aqueous humor sample collection if IOP has normalized. Alternatively, sample may be collected immediately after refill-exchange procedure at the investigator's discretion.

[i] Obtain prior to fluorescein angiography.

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

[k] For the PDS arm a maximum of four aqueous humor samples may be collected per refill interval (defined as the period beginning at either implantation or device refill-exchange procedure and ending at the visit prior to the next subsequent scheduled refill-exchange; i.e., implant insertion to Week 36; Week 40 to Week 72, etc.) either from an aqueous humor sample collection outlined here in Appendix 2 or in Appendix 6.

[l] Collect prior to or immediately after explantation.

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

[n] Dilated ophthalmoscopy examinations will also be performed in the study eye 1 day and 7 (±2) days after implant insertion (post-implant insertion Visits 1 and 2, respectively); afterward, perform dilated ophthalmoscopy examinations at each visit to monitor the implant placement and to evaluate other implant problems. *At refill-exchange visits, perform prior to and after completing refill-exchange procedure.*

[o] Refer to central reading center manual for details.

[p] In addition to the timepoints listed, implant photographs should be taken at any visit if there are concerns with implant function. Implant photos should be taken only after PDS has been implanted. *Implant photographs may be captured before and after application of topical fluorescein to the surface of the eye over the implant to monitor conjunctiva (e.g., if suspected conjunctival erosion).*

[q] Only at selected study sites. Perform pre-treatment.

[r] The use of self-administered antimicrobial ophthalmic drops are required before and after PDS implant insertion. The use of self-administered antimicrobial ophthalmic drops prior to refill-exchange is optional per the investigator's discretion but is required after refill-exchange. The use of anti-inflammatory ophthalmic drops is required after implant insertion and explantation. Dosing per standard of care.

[s] At sites that permit video recording: The implant insertion, explantation, refill-exchange, and any other ocular surgical procedures (e.g., conjunctival erosion or retinal detachment repair) performed in the study eye will be captured on video unless the study center has policies in place that prohibit these procedures from being video captured.

[t] Perform refill-exchange procedure with IxRS-assigned kit of ranibizumab 100 mg/mL. *If a refill-exchange procedure needs to be re-attempted prior to the next scheduled visit, pregnancy test for women of childbearing potential, BCVA, IOP measurement, slitlamp exam, dilated binocular indirect ophthalmoscopy, pre- and post-study treatment microbials, and post treatment finger counting test should be repeated at the unscheduled visit. Additional non-invasive ocular assessments in either eye may be performed at the investigator's discretion, including obtaining implant images. Note: Visually check implant prior to performing refill-exchange.*

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

[v] Patients with the PDS are eligible for supplemental intravitreal ranibizumab 0.5 mg if supplemental treatment criteria are met (see Section 4.3.2.3); if so, the assessments in Appendix 6 must be performed in addition to those listed here. Following supplemental intravitreal ranibizumab 0.5 mg, patients will continue with refill-exchange procedures per protocol. If a patient meets the supplemental treatment criteria within the first 3 months after implant insertion, the investigator must contact the Medical Monitor prior to administering supplemental intravitreal ranibizumab 0.5 mg treatment.

[w] 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 topical medications.

[x] *At explant visit, perform AS-OCT prior to explantation.*

Appendix 3
Schedule of Activities: Comparator Arm

Table 1 Comparator Arm: Randomization to Implant Visit and Post-Implant Insertion Visits 1 and 2

Week	R (Day 1)	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	Pre-I [a] 64	Delayed Pre-I [a] 68	Implant Visit [a]	PI-V1	PI-V2
Visit window (days)	−21 days from SCR	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	1–14D from last LD		±2
Review of inclusion and exclusion criteria	x																				
Contact IxRS	x															x	x	x	x		
Concomitant medications [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events, *adverse device effects and device deficiencies* [c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures [d]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
RetTSQs [e]	x													x							
Pregnancy test [f]	x															x	x	x			
HbA_{1c}	x			x			x			x			x			x					
Serum PK sample [g, i]																x	(x)[j]	x			
Serum ADA sample [g, i]	x															x	(x)[j]	x			
Aqueous humor sample (optional) [g, h, i, k]	x						x						x			x	(x)[j]	x			
Plasma sample (if aqueous humor sample collected) (optional) [g, h, i]	x						x						x			x	(x)[j]	x			
Blood sample for genotyping (optional)	x[j, l]																				
Best-corrected visual acuity	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Intraocular pressure [m]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x

Appendix 3: Schedule of Activities: Comparator Arm cont.

Week	R (Day 1)	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	Pre-I [a] 64	Delayed Pre-I [a] 68	Implant Visit [a]	PI-V1	PI-V2
Visit window (days)	−21 days from SCR	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	1–14D from last LD		±2
Slitlamp examination	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Dilated binocular indirect ophthalmoscopy [n]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x [n]	x	x
SD-OCT [p]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Color fundus photography [p]		x			x			x			x			x			(x) [q]	x			
Fluorescein angiography [p]								x						x			(x) [q]	x			
Lens photo (fundus reflex photograph) [p]														x							
Implant photographs [o, p]																				x	x
OCT-A, (at selected sites) [p, s]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
AS-OCT (at selected sites) [p, s]															x		x		x [o, p]	x	x
Supplemental Intravitreal ranibizumab 0.5 mg (if treatment criteria are met) [t]		x	x	x	x	x	x	x	x	x	x	x	x	x	x						
Intravitreal ranibizumab 0.5 mg injection (loading doses)																x	x	x			
Pre- and post-study-treatment antimicrobials [u]																			x		
Ranibizumab-filled implant insertion [v]																			x		
Implant insertion, refill-exchange, explantation video [w]																			x		
Implant insertion evaluation [x]																			x		

Appendix 3: Schedule of Activities: Comparator Arm cont.

Week	R (Day 1)	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	Pre-I [a] 64	Delayed Pre-I [a] 68	Implant Visit [a]	PI-V1	PI-V2
Visit window (days)	−21 days from SCR	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	1–14D from last LD		±2
Post-treatment finger-counting test [y]																x	x	x			
Follow-up call [z]																x	x	x			

ADA = anti-drug antibody; AS-OCT = Anterior Segment OCT; BCVA = best-corrected visual acuity; D = day(s); HbA_{1c} = glycosylated hemoglobin; IOP = intraocular pressure; IxRS = interactive voice or web-based response system; LD = loading dose; OCT-A = optical coherence tomography–angiography; PDS = Port Delivery System with ranibizumab; PI-V1 = post-implant insertion Visit 1 (1 day after implant insertion); PI-V2 = post-implant insertion Visit 2 (7 [±2] days after implant insertion); PK = pharmacokinetic; R = randomization; RetTSQs = Retinopathy Treatment Satisfaction Questionnaire, status version; SCR = screening; SD-OCT = spectral-domain optical coherence tomography; (x) = conditional/optional (refer to footnote).

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, unless noted otherwise. Dark gray shaded columns indicate implant visit. Light gray Week 8 Delayed Pre-Implant visit.

[a] PDS implant insertion may be delayed due to extenuating circumstances *following consultationwith the* Medical Monitor. If implant insertion surgery is delayed from Week 64 to Week 68, perform assessments as outlined in the delayed pre-implant visit Week 68 column, then perform implant visit, PI-V1, PI-V2, and subsequent Q4W study visits starting at Week 72 study visit and follow the schedule of activities as outlined here in Appendix 3 until the end of the study. Implant visit must occur within Week 64 visit window and 1–14 days from last LD. If surgery is delayed to Week 68, then implant visit must occur within the Week 68 visit window and 1–14 days from last LD.

[b] Record any concomitant medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) including pre- and post-treatment antimicrobial and anti-inflammatory medications used by the patient within 7 days prior to initiation of study treatment (intravitreal ranibizumab 0.5 mg if in PDS arm) or all medications used by the patient within 7 days prior to the randomization/Day 1 study visit (comparator arm). Protocol-specified procedural medications administered at the site will not be recorded (e.g., dilating drops; fluorescein dyes; implant insertion, refill-exchange, and explantation- procedural medications).

[c] For the comparator arm, after informed consent has been obtained but prior to the first administration of intravitreal ranibizumab 0.5 mg (either as a supplemental treatment prior to Week 60 or a loading dose at Week 60) only serious adverse events caused by a protocol-mandated intervention should be reported (see Section 5.4.2 for instructions for reporting serious adverse events). After the first administration of intravitreal ranibizumab 0.5 mg for comparator arm (either as a supplemental treatment prior to Week 60 or a loading dose at Week 60) all adverse events will be reported until the patient's final study visit. With the exception that all SARS-CoV2–related (due to viral infection or vaccine administration) adverse events will be reported for comparator arm from randomization until the patient's final study visit. Additionally, comparator arm patients that discontinue from study early, all adverse events, serious adverse events, pregnancies, and adverse events of special interest that lead to study discontinuation will be reported from randomization up to their early termination visit. *Device deficiencies will be recorded in EDC from implementation of protocol, Version 2. Adverse events and device deficiencies causality will be evaluated by a qualified ophthalmologist.* Adverse events assessed by the qualified ophthalmologist as related to implant insertion, refill-exchange, and explantation should be followed until the event resolves or the event is assessed as irreversible, chronic, or stable, even if the patient's participation in the study is over.

[d] 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.

[e] Must be interviewer-administered by site personnel (other than BCVA examiner) prior to any other study procedures. *In extenuating circumstances, the RetTSQs may be conducted by phone interview prior to an in-office study visit.*

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

[g] Collect prior to intravitreal ranibizumab injection, if applicable.

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

[i] Obtain prior to fluorescein angiography, if applicable.

[j] If implant insertion surgery is delayed to Week 68, do not collect PK, ADA, aqueous humor (optional) or plasma (optional) samples at the Week 64 visit.

[k] For the comparator arm, no more than a total of five aqueous humor sample collections may be performed prior to the PDS implantation visit (i.e., Randomization to Week 60) either from an aqueous humor sample collection outlined here in Appendix 3 or in Appendix 6.

[l] Collect at randomization or at any time during the study.

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

[n] Dilated ophthalmoscopy examinations will also be performed in the study eye 1 day and 7 (±2) days after implant insertion (post-implant insertion Visits 1 and 2, respectively); afterward, perform dilated ophthalmoscopy examinations at each visit to monitor the implant placement and to evaluate other implant problems. . *At refill-exchange visits, perform prior to and after completing refill-exchange procedure.*

[o] Performed in operating room. Upon completion of the PDS implant insertion surgery, patients will have dilated indirect ophthalmoscopy performed to monitor the implant placement and to evaluate any potential implant problems. (The recording of indirect ophthalmoscopy results using electronic data capture is not required at the implant visit).

[p] Refer to central reading center manual for details.

[q] If implant insertion surgery is delayed to Week 68, do not collect color fundus photograph and FA at the Week 64 visit.

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

[s] Only at selected study sites. Perform pre-treatment. For AS-OCT perform prior to the first administration of intravitreal ranibizumab 0.5 mg (i.e., if supplemental treatment is administered prior to, or at the Week 56 study visit, collect AS-OCT before administering supplemental treatment). *If a site has the imaging capability to perform AS-OCT angiography, they can perform this optional assessment. At selected study sites, if the site has the imaging capabilities perform AS-OCT pre- and post-PDS-implantation in operating room.*

[t] Patients in the comparator arm are eligible for intravitreal ranibizumab 0.5 mg if treatment criteria are met (see Section 4.3.2.3); if so, the assessments in Appendix 6 must be performed in addition to those listed here.

[u] The use of self-administered antimicrobial ophthalmic drops is required before and after PDS implant insertion. The use of self-administered antimicrobial ophthalmic drops prior to implant refill-exchange is optional per the investigator's discretion but is required after refill-exchange. Anti-inflammatory ophthalmic drops may be administered as well, per standard of care.

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

[w] At sites that permit video recording: The implant insertion, explantation, refill-exchange, and any other ocular surgical procedures (e.g., conjunctival erosion or retinal detachment repair) performed in the study eye will be captured on video unless the study center has policies in place that prohibit these procedures from being video captured.

[x] Upon completion of the implant insertion surgery, complete the implant insertion evaluation electronic Case Report Form to indicate surgical details of the insertion procedure.

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

[z] 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 topical medications.

Table 2 Comparator Arm: Week 68 to Final Visit, Early Termination Visit, and Explantation Visit

Week	68 [a]	72	76	80	84	88	100	Visit X (12W post refill-XCH)	Visit Y (24W post refill-XCH)	Visit Z (36W post refill-XCH)	Optional Visit [b]	Final Visit	Early Term.	Explant. Visit
Visit window (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	NA	NA	30 or 90 [c]	NA
Contact IxRS							x			x	x	x	x	x
Vital signs												x	x	x
Concomitant medications [d]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events, *adverse device effects, and device deficiencies* [e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures [f]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
RetTSQs [g]								x [h]					x	
PPPQ [g]								x [h]					x	
Pregnancy test [i]							x			x		x	x	
HbA_{1c}	x					x	x			x		x	x	
Serum PK sample [j, l]	x	(x) [k]				x	x						x	x
Serum ADA sample [j, l]	x	(x) [k]				x	x						x	x
Aqueous humor sample (optional) [j, l, m, n, o]						x	x		x	x				
Plasma sample (if aqueous humor sample collected) (optional) [j, n, o]						x	x		x	x				
Aqueous humor sample for biomarkers and ranibizumab concentration (mandatory)													x [l]	x [p]
Plasma samples for biomarkers (mandatory)													x [l]	x
Best-corrected visual acuity	x	x	x	x	x	x	x	x	x	x	x	x	x	
Intraocular pressure [q]	x	x	x	x	x	x	x	x	x	x	x	x	x	
Slitlamp examination	x	x	x	x	x	x	x	x	x	x	x	x	x	

Appendix 3: Schedule of Activities: Comparator Arm cont.

Week	68 [a]	72	76	80	84	88	100	Visit X (12W post refill-XCH)	Visit Y (24W post refill-XCH)	Visit Z (36W post refill-XCH)	Optional Visit [b]	Final Visit	Early Term.	Explant. Visit
Visit window (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	NA	NA	30 or 90 [c]	NA
Dilated binocular indirect ophthalmoscopy [r]	x	x	x	x	x	x	x	x	x	x	x	x	x	
Post-refill-exchange dilated binocular indirect ophthalmoscopy [r]							x			x				
SD-OCT [s]	x	x	x	x	x	x	x	x	x	x	x	x	x	
Fundus photography [s]			x			x	x	x	x	x		x	x	
Fluorescein angiography [s]							x			x		x	x	
Lens photo (fundus reflex photograph) [s]							x			x		x	x	
Implant photographs [s, t]	x	x	x	x	x	x	x	x	x	x		x	x	
OCT-A (at selected sites) [s, u]	x	x	x	x	x	x	x	x	x	x	x	x	x	
AS-OCT (at selected sites) [s, u, v]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pre- and post-study-treatment antimicrobials [w]							x			x				
Implant insertion, refill-exchange, explantation video [x]							x			x				x
Refill-exchange [y]							x			x				
Post-treatment finger-counting test [z]							x			x				
Supplemental intravitreal ranibizumab 0.5 mg (if supplemental treatment criteria are met) [aa]	x	x	x	x	x	x		x	x		x			
Follow-up call [bb]							x			x				

Appendix 3: Schedule of Activities: Comparator Arm cont.

ADA = anti-drug antibody; AS-OCT = Anterior-segment optical coherence tomography; BCVA = best-corrected visual acuity; Explant = explantation; HbA_{1c} = glycosylated hemoglobin; IOP = intraocular pressure; IxRS = interactive voice or web-based response system; LD = loading dose; NA = not applicable; OCT-A = optical coherence tomography-angiography; PDS = Port Delivery System with ranibizumab; PK = pharmacokinetic; PPPQ = PDS Patient Preference Questionnaire; RetTSQs = Retinopathy Treatment Satisfaction Questionnaire, status version; SD-OCT = spectral-domain optical coherence tomography; Term = termination; W = week(s); (x) = conditional/optional (refer to footnote); XCH = exchange.

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, unless noted otherwise. Shaded columns indicate refill-exchange visits.

[a] PDS implant insertion may be delayed due to extenuating circumstances *following consultation with the* Medical Monitor. If implant insertion surgery is delayed from Week 64 to Week 68, perform assessments as outlined in the delayed pre-implant visit Week 68 column, then perform implant visit, post-implant insertion Visit 1 (1 day after implant insertion), post-implant insertion Visit 2 (7 [±2] days after implant insertion), and subsequent Q4W study visits starting at Week 72 study visit and follow the schedule of activities as outlined here in Appendix 3 until the end of the study. Implant visit must occur within Week 64 visit window and 1–14 days from last LD. If surgery is delayed to Week 68, then implant visit must occur within the Week 68 visit window and 1–14 days from last LD.

[b] Perform listed assessments for optional visits after Week 76 only. For unscheduled safety assessment visits prior to Week 76, perform listed assessments in Appendix 5.

[c] Visit window of 30 (+7) days from last completed study visit or 90 (+7) days post-implant (see Section 4.6.2).

[d] Record any concomitant medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) including pre- and post-treatment antimicrobial and anti-inflammatory medications used by the patient within 7 days prior to initiation of study treatment (intravitreal ranibizumab 0.5 mg if in PDS arm) or all medications used by the patient within 7 days prior to the randomization/Day 1 study visit (comparator arm). Protocol-specified procedural medications administered at the site will not be recorded (e.g., dilating drops; fluorescein dyes; implant insertion, refill-exchange, and explantation- procedural medications).

[e] All adverse events, serious adverse events, pregnancies, and adverse events of special interest will be reported for the comparator arm after the first administration of intravitreal ranibizumab 0.5 mg (resulting from either supplemental treatment prior to Week 60 or loading dose at Week 60) through the final study visit. *Device deficiencies will be recorded in EDC from implementation of protocol version 2. Adverse events and device deficiencies causality will be evaluated by the qualified ophthalmologist.* Adverse events assessed by the qualified ophthalmologist as related to implant insertion, refill-exchange, and explantation should be followed until the event resolves or the event is assessed as irreversible, chronic, or stable, even if the patient's participation in the study is over.

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

[g] Must be interviewer-administered by site personnel (other than BCVA examiner) prior to any other study procedures. *In extenuating circumstances, may be administered by phone interview prior to in-office study visit.*

[h] These assessments should take place at Week 112 only and are not required at subsequent visits.

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

[j] Collect prior to intravitreal ranibizumab injection, if applicable.

[k] If implant insertion surgery is delayed to Week 68, collect PK and ADA samples at the Week 72 visit.

[l] Obtain prior to fluorescein angiography.

[m] To allow for IOP renormalization, collect aqueous humor sample at ≥45 minutes prior to the refill-exchange procedure. However, the refill-exchange procedure may be performed <45 minutes following aqueous humor sample collection if IOP has normalized. Alternatively, sample may be collected immediately after refill-exchange procedure at the investigator's discretion.

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

[o] For the comparator arm patients after they have received the PDS implant, no more than a total of four aqueous humor samples may be collected per refill interval (i.e., from implant insertion to Week 88, etc.) either from an aqueous humor sample collection outlined in Appendix 3 or in Appendix 6.

[p] Collect prior to or immediately after explantation.

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

[r] Dilated ophthalmoscopy examinations will also be performed in the study eye 1 and 7 (±2) days after implant insertion (post-implant insertion Visits 1 and 2, respectively); afterward, perform dilated ophthalmoscopy examinations at each visit to monitor the implant placement and to evaluate other implant problems. *At refill-exchange visits, perform prior to and after completing refill-exchange procedure.*

[s] Refer to central reading center manual for details.

[t] In addition to the timepoints listed, implant photographs should be taken at any visit if there are concerns with implant function. Implant photos should be taken only after PDS has been implanted. *Implant photographs may be captured before and after application of topical fluorescein to the surface of the eye over the implant to monitor conjunctiva (e.g., if suspected conjunctival erosion).*

[u] Only at selected study sites. Perform pre-treatment. *If a site has the imaging acpability to perform AS-OCT angiography, they can perform this optional assessment.*

[v] At explant visit, perform AS-OCT prior to explant.

[w] The use of self-administered antimicrobial ophthalmic drops are required before and after PDS implant insertion. The use of self-administered antimicrobial ophthalmic drops prior to refill-exchange is optional per the investigator's discretion but is required after implant refill-exchange. Anti-inflammatory ophthalmic drops may be administered as well, per standard of care.

[x] At sites that permit video recording: The implant insertion, explantation, refill-exchange, and any other ocular surgical procedures (e.g., conjunctival erosion or retinal detachment repair) performed in the study eye will be captured on video unless the study center has policies in place that prohibit these procedures from being video captured.

Appendix 3: Schedule of Activities: Comparator Arm cont.

[y] Perform refill-exchange procedure with IxRS-assigned kit of ranibizumab 100 mg/mL. *If a refill-exchange procedure needs to be re-attempted prior to the next scheduled visit, pregnancy test for women of childbearing potential, BCVA, IOP measurement, slitlamp exam, dilated binocular indirect ophthalmoscopy, pre- and post-study treatment microbials, and post treatment finger counting test should be repeated at the unscheduled visit. Additional non-invasive ocular assessments in either eye may be performed at the investigator's discretion, including obtaining implant images.*

Note: Visually check implant prior to performing refill-exchange

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

[aa] Patients with the PDS are eligible for supplemental intravitreal ranibizumab 0.5 mg if supplemental treatment criteria are met (see Section 4.3.2.3); if so, the assessments in Appendix 6 must be performed in addition to those listed here. Following supplemental intravitreal ranibizumab 0.5 mg, patients will continue with refill-exchange procedures per protocol. If a patient meets the supplemental treatment criteria within the first 3 months after implant insertion, the investigator must contact the Medical Monitor prior to administering supplemental intravitreal ranibizumab 0.5-mg treatment.

[bb] 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.

Appendix 4
Schedule of Activities: New Implant Insertion following Implant Removal

The assessments listed below will be performed when a patient undergoes a new implant insertion (post-implant removal). Patients will attend scheduled visits for safety assessments, as described below, the day immediately after the implant insertion procedure (post–re-implant insertion Visit 1), 7 (±2) days (post–re-implant insertion Visit 2) and 28 (±7) days (post–re-implant insertion Visit 3). After the post–re-implant Visit 3, patients will resume attending study visits according to the main schedule of activities (see Appendix 2 and Appendix 3).

Assessment	*Explant and Re-Implant Insertion Visit* [a]	*Post-Re-Implant Insertion Visit 1*	*Post-Re-Implant Insertion Visit 2*	*Post-Re-Implant Insertion Visit 3*
Visit window		*1 day after re-implant insertion visit*	*7 (± 2) days after re-implant insertion visit*	*28 (± 7) days after re-implant insertion visit*
Contact IxRS [b]	x			
Adverse events, adverse device effects, and device deficiencies [c]	x	x	x	x
Concomitant medications	x	x	x	x
Concurrent ocular procedures [d]	x	x	x	x
Pregnancy test [e]	x			
Serum PK sample	x			
Serum ADA sample	x			
Aqueous humor sample for biomarkers and ranibizumab concentration (optional)	x [f]			
Plasma samples for biomarkers	x			
BCVA		x	x	x
IOP [g]	x [h]	x	x	x
Slit-lamp examination		x	x	x

Appendix 4: Schedule of Activities: New Implant Insertion following Implant Removal cont.

Assessment	Explant and Re-Implant Insertion Visit [a]	Post-Re-Implant Insertion Visit 1	Post-Re-Implant Insertion Visit 2	Post-Re-Implant Insertion Visit 3
Visit window		1 day after re-implant insertion visit	7 (± 2) days after re-implant insertion visit	28 (± 7) days after re-implant insertion visit
Dilated indirect ophthalmoscopy [h]		x	x	x
SD-OCT [i]			x	x
AS-OCT [j, k]		x	x	x
Pre- and post-study treatment antimicrobials [l]	x			
Ranibizumab filled implant insertion [m]	x			
Implant insertion video [n]	x			
Post-implantation IOP measurement [o]	x			
Implant insertion evaluation [p]	x			
Implant photographs		x	x	x

ADA =anti-drug antibody; AS-OCT =anterior segment optical coherence tomography; AS-OCT-A; BCVA =best-corrected visual acuity; EDC =electronic data capture; PDS =Port Delivery System; PK =pharmacokinetic; IOP =intraocular pressure; IxRS =interactive voice or web-based response system; SD-OCT =spectral-domain optical coherence tomography; Q36W =every 36 weeks.

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.

[a] *If the last study visit was completed more than 4 weeks (28 days) prior to the explantation/re-implantation scheduled date, an additional visit (as an unscheduled visit, Appendix 5) must be performed. After re-implantation, patients will complete post–re-implantation study visits and continue with the originally scheduled Q36W refill-exchange procedures per protocol.*

[b] *IxRS will be contacted at the re-implant visit for the dispensation of the PDS devices and the ranibizumab 100 mg/mL.*

[c] *Adverse events, adverse device effects, and device deficiencies causality will be evaluated by the qualified ophthalmologist.*

[d] *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.*

[e] *Perform locally the urine pregnancy test for women of childbearing potential, including patients who have had tubal ligation. If the urine pregnancy test is positive, collect serum pregnancy sample. If the serum pregnancy test is positive, do not perform implant insertion procedure.*

[f] *Collect prior to explantation or immediately after re-implantation procedure.*

[g] *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.*

[h] *Should be performed in the surgical center using indentation tonometry for the study eye only prior to the implant insertion surgery.*

[i] *Perform prior to explantation and upon completion of implant insertion. Patients will have dilated indirect ophthalmoscopy performed to monitor the implant placement and to evaluate any potential implant problems (capturing the results of the dilated indirect ophthalmoscopy findings on EDC is not needed at re-implant visit). Perform dilated indirect ophthalmoscopy examinations to monitor the implant for any potential implant problems.*

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

[k] *Only at selected study sites. Perform pretreatment. If a site has the imaging capability to perform AS-OCT-A, perform this optional assessment at the investigator's discretion.*

[l] *The pre- and post-implant insertion use of self-administered antimicrobials is required. Anti-inflammatory drops post-implant insertion are required (see Appendix 17).*

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

[n] *For sites that permit video recording.*

[o] *IOP 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 in the surgical center and will be treated according to the designated physician's clinical judgment. If applicable, the adverse event will be reported.*

[p] *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.*

Appendix 5
Unscheduled Safety Assessment Visit, Post-Study Treatment Discontinuation Visits, or Post-Explantation Safety Visits

The assessments listed below will be performed at the following study visits:

- Unscheduled safety assessment visits (applicable prior to Week 88; for optional visits after Week 88, perform listed assessments in Appendix 2 and Appendix 3
- Study visits for patients who discontinue study treatment but remain in the study
- Safety assessment visits following explantation (at 1, 7 [±2], 30 [±7], and 60 [±7] days post-explantation).

Other assessments, listed in Appendix 2 and for specific study visits, may be performed at the discretion of the investigator for patients who discontinue study treatment.

	Unscheduled Safety Assessment Visit [a]	Post–Study Treatment Discontinuation Visits [b]	Post-Explantation Safety Visits [c]
Vital signs (blood pressure and pulse) [c]	x		x
BCVA (assessed on ETDRS chart at a 4-meter starting distance) [d]	x	x	x
Slitlamp examination	x	x	x
Dilated binocular indirect high-magnification ophthalmoscopy	x	x	x
Intraocular pressure [e]	x	x	x
SD-OCT [f]	x	x	x[g]
Adverse events, *adverse device effects, and device deficiencies* [h]	x	x	x
Concurrent ocular procedures	x	x	x
Serum PK sample (optional) [i]	*x*		

BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; *PK = pharmacokinetic*; SD-OCT = spectral-domain optical coherence tomography.

[a] An unscheduled safety assessment visit is applicable to any enrolled study patient up to Week 64. If an unscheduled safety assessment visit is determined to be necessary by the physician, perform all listed assessments. Ocular assessments may be performed on one eye only, except BCVA testing which must be performed on both eyes. For optional visits after Week 88, perform listed assessments in Appendix 2 and Appendix 3.

[b] At a post-explantation visit, perform all listed assessments; ocular assessments may be performed on the study eye only (and SD-OCT images do not need to be sent to the reading center), except for BCVA testing which must be performed on both eyes.

[c] Perform at 1, 7 [± 2], 30 [± 7], and 60 [± 7] days post-explantation.

[d] BCVA assessment must be performed in both eyes by masked visual acuity assessor. Perform finger-counting test followed by hand motion and light perception tests when necessary.

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

[f] Required in study eye only. Refer to the central reading center manual for details.

[g] SD-OCT is optional at post-explantation safety assessment visits at 1 day and 7 (±2) days post-explantation.

[h] *Assessment of* causality *for adverse event and device deficiency* to be evaluated by a qualified ophthalmologist.

[i] *A serum PK sample (optional) should be collected prior to fluorescein angiography (if applicable) and shipped per the central laboratory manual. Serum PK samples are collected for exploratory research to support future drug development and will not inform decisions on patient management.*

Appendix 6
Additional Assessments *If* Supplemental Treatment Criteria *or* *Eligibility* Are Met

PDS patients will be eligible for supplemental treatment with intravitreal ranibizumab (0.5-mg intravitreal injections of 10-mg/mL formulation) at each non-refill-exchange *every 4 weeks (*Q4W*)* study visit after implant insertion. Beginning at Week 88, patients will switch to mandatory visits *every 12 weeks (*Q12W*)*. Optional visits may be added between each mandatory Q12W visit at the investigator's discretion.

Comparator arm patients will be eligible for treatment with supplemental intravitreal ranibizumab 0.5 mg at each Q4W visit starting after randomization until Week 56. Following implant insertion at Week 64, comparator arm patients will be eligible for supplemental treatment with intravitreal ranibizumab 0.5 mg as described above.

If a patient meets the supplemental treatment criteria (see Section 4.3.2.3) or meets the treatment eligibility criteria (in comparator arm before Week 60) and the investigator decides to administer treatment, the following assessments must be performed in addition to the assessments listed in Appendix 2 (patients in the PDS arm) or Appendix 3 (patients in the comparator arm).

If treatment cannot be administered at the end of the visit, patients will be asked to return within 7 days to receive supplemental treatment (see Section 4.3.2.3). Assessments such as pregnancy test for women of childbearing potential and intra-ocular pressure measurement in the study eye should be repeated at the visit, prior to administering supplemental treatment. Post-treatment assessments, such as the finger-counting test, hand motion, and light perception tests (when necessary), and the follow-up call must also be done. Additional non-invasive ocular assessments in either the study eye or fellow eye may be performed at the investigator's discretion.

Alternatively, additional assessments (see Table 1) can be delayed to the visit when supplemental treatment will be administered.

Table 1 Supplemental Treatment Assessments to Be Performed

Assessments to Be Performed *If* Treatment Criteria *or Eligibility* Are Met and Treatment Administered	
Pregnancy test [a]	x
Serum PK sample [b]	x [c]
Aqueous humor sample [b, d]	x [c]
Plasma sample for biomarkers [b, e]	x [c]
Intravitreal ranibizumab 0.5 mg	x
Post-treatment finger-counting test [f]	x
Follow-up call [g]	x

PK = pharmacokinetic.

[a] For women of childbearing potential, including those who have had tubal ligation, urine pregnancy test will be performed locally prior to supplemental treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Do not administer the supplemental treatment until the final results are available. If the serum pregnancy test is positive, do not administer the supplemental treatment.

[b] Collect sample prior to intravitreal ranibizumab 0.5 mg.

[c] Sample should be collected at the supplemental treatment visit and at the subsequent study visit.

[d] **For *patients in* the PDS arm**, a maximum of four aqueous humor per refill interval (defined as the period beginning at either implantation or device refill-exchange procedure and ending at the visit prior to the next subsequent scheduled refill, i.e., implant insertion to Week 36; Week 40 to Week 72, etc.) either from an aqueous humor sample collection outlined in Appendix 2 or Appendix 6.
For *patients in* the comparator arm, if a patient does not have the PDS implanted and a supplemental treatment is administered, it is per investigator's discretion to collect the aqueous humor sample outlined here in Appendix 6. A maximum of five aqueous humor sample collections may be performed prior to the PDS implantation visit (i.e., Randomization to Week 60) either from an aqueous humor sample collection outlined in Appendix 2 or Appendix 6.
For *patients in* the comparator arm, patients after the PDS has been implanted, a maximum of four aqueous humor samples may be collected per refill interval (i.e., from implant insertion to Week 88, etc.) either from an aqueous humor sample collection outlined in Appendix 2 or Appendix 6.

[e] Plasma sample for biomarkers and serum PK samples will only be collected, if supplemental treatment is administered and *aqueous humor* sample is collected.

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

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

Appendix 7
Best-Corrected Visual Acuity Testing

SCOPE

Best-corrected visual acuity (BCVA) will be measured by trained and certified personnel at the study sites. *At each study visit, Early Treatment Diabetic Retinopathy Study (ETDRS) trial frame refraction will be performed first, followed by BCVA measurement (for more information, refer to the Visual Acuity Specifications Manual).*

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

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

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

BCVA will be measured at the intervals specified in the protocol (see Appendix 1, Appendix 2, and Appendix 3).

EQUIPMENT

The following is needed at minimum to conduct the examination:

- Examination lane of adequate dimensions to allow testing at required distances
- Standard chair with a firm back
- Set of three Precision Vision™ or Lighthouse distance acuity charts (modified ETDRS Charts 1, 2, and R)
- Retro-illuminated box
- Trial frame
- Trial lens set

TRAINING AND CERTIFICATION

A BCVA specifications document, procedure manual, and training materials will be provided to the investigational sites, and BCVA examiner certification will be obtained. The BCVA examination room also must be certified before any BCVA examinations

are performed. If new BCVA personnel or BCVA rooms are added to the study, certification must be obtained prior to performing study assessments.

Appendix 8
Grading Scales for Anterior Chamber Flare or Cells and Vitreous Cells

GRADING SCALE FOR ANTERIOR CHAMBER FLARE OR CELLS

Flare	
Grade	**Description**
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

Cells [a]	
Grade	**Number of Cells in Field**
0	<1
0.5+	1–5
1+	6–15
2+	16–25
3+	26–50
4+	>50

Modified from: Foster CS, Kothari S, Anesi SD, et al. The Ocular and Uveitis Foundation preferred practice patterns of uveitis management. Surv Opthalmol 2016;61:1–17.

[a] Field size is a 1-mm slit beam.

GRADING SCALE FOR VITREOUS CELLS

Grade	Number of Vitreous Cells
0	No cells
0.5+	0–10
1+	11–20
2+	21–30
3+	31–100
4+	>101

Modified from: Foster CS, Kothari S, Anesi SD, et al. The Ocular and Uveitis Foundation preferred practice patterns of uveitis management. Surv Opthalmol 2016;61:1–17.

Appendix 9
Grading Scales for Vitreous Hemorrhage

GRADING SCALE FOR VITREOUS HEMORRHAGE DENSITY

Grade	Description
None (0)	Retina is visible.
Trace	Retina is visible and red blood cells are visible only on slitlamp examination.
1+	Retinal detail is visible; some hemorrhage is visible by ophthalmoscopy.
2+	Large retinal vessels are visible, but central retinal detail is not visible by ophthalmoscopy.
3+	Red reflex is visible, but no central retinal detail is seen posterior to the equator by ophthalmoscopy.
4+	No red reflex by ophthalmoscopy.

VITREOUS HEMORRHAGE FUNCTIONAL GRADING SCALE

Grade	Description
1	≤15 letter BCVA loss from the previous visit
2	16–30 letter BCVA loss from the previous visit
3	>30 letter BCVA loss from the previous visit to hand motion
4	Light Perception or worse

Appendix 10
Fundus Photography

SCOPE

Fundus photography (FP) will be taken by trained personnel at the study sites at the intervals specified in the protocol.

FP imaging will be performed for each patient at the intervals specified in the protocol (see Section 4.5.4, Appendix 1, Appendix 2, and Appendix 3) 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 central reading center manual.

PROCEDURE

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

Appendix 11
Fluorescein Angiography

SCOPE

Fluorescein angiography (FA) will be performed at the study sites by trained personnel who are certified by the central reading center. The FA images will be obtained at the intervals specified in the protocol (see Section 4.5.4, Appendix 1, Appendix 2, and Appendix 3), will be forwarded to the central reading center for analysis and/or storage and will be *subsequently* transferred to Roche.

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 material. Photographers, systems, and software will be certified prior to obtaining patient angiograms.

Appendix 12
Spectral-Domain Optical Coherence Tomography

SCOPE

Spectral-domain optical coherence tomography (SD-OCT) will be performed on both eyes at the study sites by trained personnel who are certified by the central reading center. SD-OCT imaging will be performed for each patient at the intervals specified in the protocol (Section 4.5.5, Appendix 1, Appendix 2, and Appendix 3), will be forwarded to the central reading center for analysis and/or storage, and will later be transferred to Roche.

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.

Note: Central subfield thickness is defined as the average thickness of the central 1 mm circle of the ETDRS grid centered on the fovea from inner limiting membrane to Bruch's membrane (see *the* central reading center manual).

Appendix 13
Implant Photographs

SCOPE

Implant photographs will be taken by trained personnel at the study sites at the intervals specified in the protocol.

Implant imaging will be performed for implant patients only at each study visit as specified in the protocol (see Section 4.5.5, Appendix 1, Appendix 2, and Appendix 3), will be forwarded to the central reading center for analysis and/or storage, and will later be transferred to Roche. Analysis (if applicable) of implant 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 central reading center manual.

PROCEDURE

The central reading center will provide a study manual and training material, *including further information on obtaining implant photographs after the topical application of fluorescein*. The photographer and equipment will be certified by the reading center before any study images are taken.

Appendix 14
Optical Coherence Tomography-Angiography (at Selected Sites)

SCOPE

Optical coherence tomography (OCT) angiography will be performed on both eyes only at selected study sites that have OCT-angiography equipment by trained personnel who are certified by the central reading center. OCT-angiography imaging will be performed for each patient at the intervals specified in the protocol (see Section 4.5.5, Appendix 1, Appendix 2, and Appendix 3), will be forwarded to the central reading center for analysis and/or storage, and will later be transferred to Roche.

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

EQUIPMENT

Equipment utilized during this trial is described in the central reading center manual. The ability to transfer images to electronically export digital files is required (i.e., no printed OCT-angiography images will be sent to the central reading center).

PROCEDURES AND CERTIFICATION

The central reading center will provide the study manual and training materials. OCT angiography operators, systems, and software will be certified prior to any evaluation of patients.

Appendix 15
Anterior Segment Optical Coherence Tomography

SCOPE

Anterior *segment optical coherence tomography* (AS-OCT), *including optional AS-OCT angiography,* will be performed on the study eye only at selected study sites *or at sites per investigator discretion* that have *this imaging capability. Imaging will be performed* by trained personnel who are certified *or in the process of being certified* by the central reading center.

AS-OCT imaging will be performed for each patient at the intervals specified in the protocol *Schedule of Activities in Appendix 2, and Appendix 3 or at any visit per investigator discretion* (see Section 4.5.5, Appendix 2, and Appendix 3). *The AS-OCT images* will be forwarded to the central reading center for analysis and/or storage and will later be transferred to Roche.

See central reading center manual *for additional details.*

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 AS-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. AS-OCT operators, systems, and software will be certified *or in the process of certification* prior to any evaluation of patients.

Appendix 16
Sample Collection and Shipping

BIOLOGICAL SAMPLES

Samples for assessment of laboratory safety (hematology, serum chemistry, coagulation) and urinalysis will be collected at screening visit.

A urine pregnancy test will be collected and performed prior to each treatment for women of childbearing potential, including those who have had tubal ligation. If positive, serum pregnancy test will be performed. If the serum pregnancy test is positive, the study treatment will be discontinued.

Serum for assessment of ranibizumab concentrations (pharmacokinetics) and anti-ranibizumab antibodies will be collected at the timepoints specified in the schedules of activities (Appendix 2, Appendix 3, and Appendix 5).

Mandatory aqueous humor (see below for sample collection), plasma, and serum PK samples will be collected at supplemental treatment and at the subsequent visit, at early termination, and at explantation visits, if explantation is needed.

In addition, for *patients* who provide consent, optional aqueous humor, plasma, and serum PK samples will be collected at the timepoints specified in the schedules of activities (Appendix 2 and Appendix 3).

For *patients* who provide consent to the Research Biosample Repository (RBR), an optional whole blood sample will be collected at the randomization visit for genotyping (see Appendix 2 and Appendix 3). The laboratory safety (hematology, serum chemistry, coagulation, and urinalysis), serum pregnancy (as required), aqueous humor, serum, and plasma samples will be shipped and analyzed by the central laboratory, Sponsor, or a selected designee, except for the urine pregnancy test which will be analyzed at study site's local laboratory. All necessary transfer tubes, labels, forms, and shipping supplies will be provided by the central laboratory.

ANTERIOR CHAMBER (AQUEOUS HUMOR) SAMPLE COLLECTION

Aqueous humor samples will be required to be collected when a patient with the PDS implant receives supplemental intravitreal ranibizumab injection and at the subsequent visit. A patient, in either study arm, may also consent to optional aqueous humor sampling, which would occur at the timepoints listed in Appendix 2, and Appendix 3. Unscheduled sampling may be performed at other or additional planned visits at the discretion of the investigator in agreement with the participating patient.

The optional aqueous humor paracentesis samples will be collected from patients who consent to the procedure and sample acquisition. The aqueous humor sample collection

consists of an anterior chamber paracentesis (removing 0.05 to 0.1 mL of fluid from the anterior chamber of the eye).

The anterior chamber paracentesis will be performed by a qualified physician by placing a drop of topical anesthetic on the cornea, passing a 30-gauge needle through the limbus into the anterior chamber, and removing 0.05 to 0.1 mL of aqueous humor fluid.

Samples will be collected with the kit provided by central laboratory and shipped on dry ice to the central laboratory, Sponsor, or a selected designee as soon as possible after the draw.

For administration of intravitreal injection following the collection of the aqueous humor sample, if the investigator chooses to use subconjunctival lidocaine anesthetic, it must be injected subconjunctivally prior to study treatment.

IMPLANTS *OR IMPLANT COMPONENTS* WITH CONTENTS

Explanted implants *or refill-exchange needles* containing ranibizumab drug product will be preserved for potential analysis upon explant procedure *or refill-exchange procedure*. A method to retrieve the contents from explanted implants is in place and protocols to characterize drug product are under development. In addition, the explanted implants may undergo physical inspection and/or functional testing. *All necessary materials to return explanted implants and refill-exchange needles will be provided to each site. Please refer to the device deficiencies and study drug complaints manual for the clinical sites document.*

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 17
Topical Antimicrobial and Anti-*I*nflammatory Ophthalmic Drops Administration Schedule

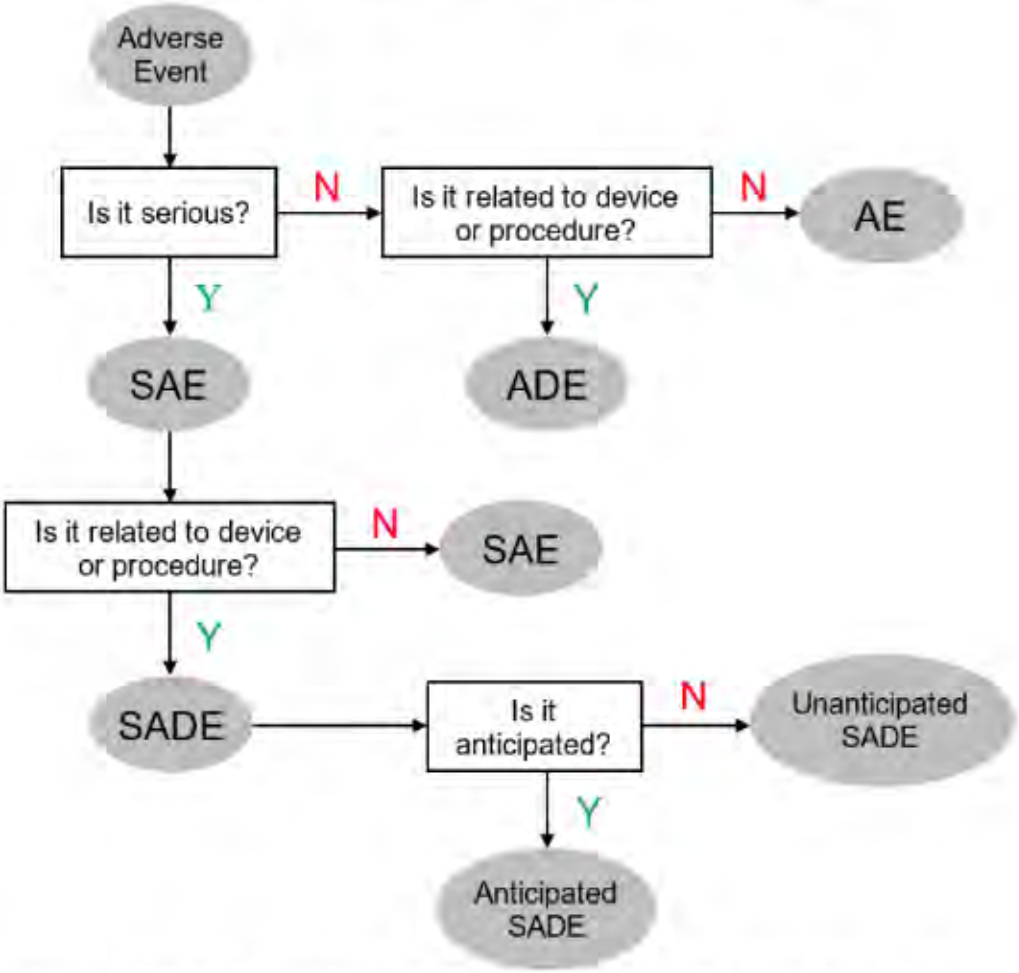
		Prior to Procedure	After Procedure
Implant Insertion	Antimicrobial ophthalmic drops	Required: 4 times within 24 hours (every 6 hours) prior to implant insertion	Required: dosing per standard of care
	Anti-inflammatory *o*phthalmic drops	Recommended – topical NSAID beginning 7 days prior to procedure per standard of care	Required: dosing per standard of care Recommended: 4-week course of topical NSAID per standard of care
Refill-exchange	Antimicrobial ophthalmic drops	Optional: 4 times within 24 hours (every 6 hours) prior to refill-exchange	Required: dosing per standard of care
Explantation	Antimicrobial ophthalmic drops	Required: 4 times within 24 hours (every 6 hours) prior to explantation	Required: dosing per standard of care
	Anti-inflammatory *o*phthalmic drops	Not required	Required: topical steroid dosing per standard of care Optional: topical NSAID per standard of care
Intravitreal Injection	Antimicrobial ophthalmic drops	Optional: dosing per standard of care	Optional: dosing per standard of care

NSAID=*non-steroidal* anti-inflammatory drug.

Notes: Suggested topical broad spectrum antimicrobial ophthalmic drops include ofloxacin ophthalmic solution (Ocuflox®), gatifloxacin ophthalmic solution (Zymar®), moxifloxacin ophthalmic solution (Vigamox®), or trimethoprim-polymyxin B ophthalmic solution (Polytrim®).

Topical anti-inflammatory ophthalmic drops *may be administered to patients at the physician's* discretion.

Appendix 18
Adverse Event Categorization Guidelines



ADE=adverse device effect; AE=adverse event; N=no; SADE=serious adverse device effect; SAE=serious adverse event; Y=yes.

REFERENCE

International Organization for Standardization. Clinical investigation of medical devices for human subjects-Good clinical practice (ISO Standard; No. 14155:2020). https://www.iso.org/standard/71690.html

Appendix 19
Port Delivery System with Ranibizumab

INTRODUCTION

The Port Delivery System with ranibizumab(PDS) is a novel drug delivery system that consists of an intraocular implant, a customized formulation of ranibizumab for PDS (100 mg/mL), and four ancillary devices used to fill, insert, refill, and explant the implant (i.e., an initial fill needle, an insertion tool assembly a refill needle, and an explant tool respectively), as shown in Figure 1 and described in Table 1. The PDS implant is a refillable, permanent intraocular device uniquely designed for the continuous delivery of ranibizumab (100 mg/mL). The PDS is designed to maintain therapeutic drug concentrations in the vitreous for longer durations than the available anti-vascular endothelial growth factor treatments administered by intravitreal injection. The primary mode of action of the PDS is provided by ranibizumab.

Figure 1 Port Delivery System Components

Table 1 Device Constituents of the PDS

Device	Purpose
Implant	Provides continuous release of ranibizumab to the vitreous over time The implant is intended to be permanent
Insertion tool (IT) assembly	Facilitates handling of the implant during initial filling and implant procedures (consists of an IT handle and IT carrier)
Initial fill needle	Fills the implant with ranibizumab prior to insertion
Refill needle	Refills (in situ) the implant with ranibizumab when needed
Explant tool	Grasps and securely holds the implant flange during explantation (if needed)

IT = insertion tool; PDS = Port Delivery System with ranibizumab.

MANUFACTURER

The PDS device manufacturing processes, including sterilization validation, are shown in *Table 2. The devices are manufactured by Phillips-Medisize, LLC in Menomonie, Wisconsin, USA. Phillips-Medisize is an ISO 13485-certified and -approved supplier managed under the Sponsor's internal document, "GSP119 GxP Supplier Management."*

Table 2 PDS Manufacturing Processes

PDS Component	*Primary Manufacturing Processes*	*Manufacturing Supplier*	*Sterilization and Process and CMO*
Implant	*Injection molding, heat swaging, adhesive bonding, assembly*	*Phillips-Medisize, LLC*	*EO; Sterigenics (implant and IT are packaged and sterilized together)*
Insertion tool	*Injection molding, assembly, and packaging*		
Initial fill needle	*Injection molding, assembly, and packaging*		*E-beam; Steri-Tek*
Refill needle	*Injection molding, assembly, and packaging*		*E-beam; Steri-Tek*
Explant tool	*Injection molding, assembly, and packaging*		*E-beam; Steri-Tek*

CMO =contract manufacturing organization; E-beam =electron beam; EO =ethylene oxide; PDS =Port Delivery System with ranibizumab; IT =insertion tool.

PDS DEVICE MODEL NUMBERS

Table 3 lists the model numbers of the to-be-commercialized devices that will be used in this clinical study.

Table 3 PDS Device Model Numbers and Classification

Device	Classification per MDR (EU) 2017/745	To-be-Commercial Devices Model Number
Implant	Class III	10228592
Insertion tool	Class IIa (IT Handle), Class Is (IT Carrier)	
Initial fill needle	Class Is	10214582
Refill needle	Class IIb	10214417
Explant tool	Class IIa	10214585

MDR = Medical Device Regulation; PDS =Port Delivery System with ranibizumab

DEVICE TRACEABILITY

Please refer to Section 4.3.3, Investigational Device Handling and Accountability, in the clinical study protocol as well as the pharmacy manual for information on device handling and traceability during and after the clinical study.

INTENDED USE STATEMENT

The PDS is intended for intravitreal delivery of ranibizumab for the treatment of neovascular age- related macular degeneration, diabetic macular edema, or diabetic retinopathy.

INTENDED PATIENT POPULATION

Please refer to Section 3.3.2 Rationale for Patient Population, in the clinical study protocol for specific population inclusion and exclusion criteria.

DEVICE CATEGORIZATION BY NATURE AND DURATION OF BODY CONTACT

Table 4 lists device categorization by nature and duration of body contact.

Table 4 Device Categorization by Type of and Duration of Body Contact per ISO 10993

Device	*Category*	*Intended Use*	*Contact*	*Contact Duration*
Implant	*Implant device*	*Implantable device used to provide continuous delivery of ranibizumab PDS drug product to the eye over an extended period*	*Tissue [a] and bone*	*C-permanent (≥30 days)*
Insertion tool	*Surface device*	*Tool used to hold the implant during the implantation process*	*Breached or compromised surface* *Potential contact with the conjunctiva and sclera during the <1-hour surgical procedure.*	*A-limited (≤24 hours)*
Initial fill needle (IFN)	*Externally communicating medical device*	*The IFN will have no contact with patient but will contact the drug during the initial fill process prior to implantation.*	*Tissue [a], bone, and dentin*	*A-limited (≤24 hours)*
Refill needle (RFN)	*Externally communicating medical device*	*Tool used to refill and exchange the contents of the implant with drug in situ* *RFN punctures with the refill needle in the conjunctiva during the refill process*	*Tissue [a], bone, and dentin*	*A-limited (≤ 24 hours)*
Explant tool	*Surface device*	*Tool used to remove implant from eye, when needed* *Potential contact with the conjunctiva and sclera during the <1-hour surgical procedure*	*Breached or compromised surface*	*A-limited (≤24 hours)*

IFN =initial fill needle; ISO =International Organization for Standardization; PDS =Port Delivery System with ranibizumab; RFN =refill needle

[a] *Tissue includes tissue fluids and subcutaneous spaces.*

TRAINING

Please refer to Section 3 Study Design, in the clinical study protocol for a summary of the necessary training and experience needed to use the PDS.

PDS-SPECIFIC PROCEDURES

The PDS devices are intended to be used as a system in the following three PDS-specific procedures:

- *Initial fill and implant procedure*
- *Refill-exchange procedure*
- *Implant explantation procedure (if needed)*

The surgical procedures involved in the use of the investigational devices are detailed in the instructions for use (IFU) document, as well as the PDS Investigator's Brochure.

ADDITIONAL INFORMATION

For additional information about the PDS devices, please refer to the PDS Investigator's Brochure and Instructions for Use.

Signature Page for Protocol - GR41675 Pavilion - SUSVIMO - v4 - Global/Core - Pu
System identifier: RIM-CLIN-442557

Approval Task	[redacted] Company Signatory 10-Jun-2022 23:12:57 GMT+0000