STATISTICAL ANALYSIS PLAN

STUDY 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)**
STUDY NUMBER:	GR41675
STUDY NAME:	Pavilion
VERSION NUMBER:	1.0
TEST PRODUCT:	Port Delivery System with ranibizumab (RO4893594)
EUDRACT NUMBER:	Not applicable
IND NUMBER:	113552
NCT NUMBER:	NCT04503551
PLAN PREPARED BY:	[redacted], Ph.D

STATISTICAL ANALYSIS PLAN APPROVAL

SPONSOR:	F. Hoffmann-La Roche Ltd
LEGAL REGISTERED ADDRESS:	Grenzacherstrasse 124 4070 Basel, Switzerland
DATE FINAL:	See electronic date stamp on the last page of this document.

STATISTICAL ANALYSIS PLAN VERSION HISTORY

This Statistical Analysis Plan (SAP) was developed based on Roche SAP model document Version 2, 26 October 2020.

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
1.0	|see electronic date stamp on title page|	Version 4, 10 June 2022

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
ADA	anti-drug antibody
ADE	adverse device effect
AE	adverse event
AESI	adverse events of special interest
ASNV	anterior segment neovascularization
AUC	area under the concentration-time curve
BCVA	best-corrected visual acuity
CCOD	clinical cut-off date
CI-DME	center-involved diabetic macular edema
CI	confidence interval
Cmax	maximum serum concentration
CMH	Cochran–Mantel–Haenszel
CST	central subfield thickness
COVID-19	coronavirus disease of 2019
DME	diabetic macular edema
DR	diabetic retinopathy
DRB	Data Review Board
DRSS	Diabetic Retinopathy Severity Scale
eCRF	electronic Case Report Form
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
HbA_{1c}	glycosylated hemoglobin
HR	hazard ratio
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IOP	intraocular pressure
ITT	intent–to–treat
IxRS	interactive web/mobile-based response system
MMRM	mixed-effect model for repeated measures
nAMD	neovascular age-related macular degeneration
NPDR	nonproliferative diabetic retinopathy
PDR	proliferative diabetic retinopathy
PDS	Port Delivery System with ranibizumab
PK	pharmacokinetic
PPPQ	PDS Patient Preference Questionnaire

PRP	panretinal photocoagulation
PT	preferred term
Q4W	every 4 weeks
Q36W	every 36 weeks
RetTSQs	Retinopathy Treatment Satisfaction Questionnaire, status version
SADE	serious adverse device effect
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory coronavirus 2
SD	standard deviation
SD-OCT	spectral-domain optical coherence tomography
SMQ	standardized MedDRA query
SOC	System Organ Class
SUN	Standardization of Uveitis Nomenclature
$t_{1/2}$	half-life
VA	visual acuity
VEGF	vascular endothelial growth factor

1. INTRODUCTION

Diabetic retinopathy (DR) can be a chronic and debilitating retinal vascular disease secondary to diabetes mellitus and is a leading cause of loss of visual function 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).

Progression of DR can lead to subsequent loss of visual function 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- vascular endothelial growth factor (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). The current therapeutic options for patients with severe non-proliferative DR include observation, laser treatment (pan-retinal photocoagulation or focal laser treatment), intravitreal steroids, and anti-VEGF treatment. Anti-VEGF therapy has been demonstrated to have superior functional outcomes compared to laser treatment but requires frequent injections and monitoring and has associated risks including retinal detachment and endophthalmitis. There is an opportunity for a sustained delivery of ranibizumab over 36 weeks to reduce burden for the patient and their healthcare system (Flaxel et al. 2020).

The Port Delivery System with ranibizumab (PDS) is a drug delivery technology that allows physicians to use ranibizumab with a continuous drug delivery mechanism without altering its chemistry. It consists of an ocular implant, 4 ancillary devices (initial fill needle, insertion tool assembly, refill needle, and explant tool), and a customized formulation of ranibizumab tailored for continuous delivery. The PDS (100 mg/mL) with every 24 weeks (Q24W) retreatment (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 Neovascular (wet) Age-related Macular Degeneration (nAMD) who have previously responded to at least two intravitreal injections of a Vascular Endothelial Growth Factor (VEGF) inhibitor medication. Refer to the U.S. Package Insert for details (SUSVIMO [package insert] 2021).

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, 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 and potential complications associated with intermittent intravitreal injections of aVEGFs. 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 purpose of this document is to provide details of the planned analyses for Study GR41675 (Pavilion). The analyses and endpoints specified in this document supersede the analysis plan described in the Study Protocol.

The Sponsor sought feedback on the draft Statistical Analysis Plan (SAP) of Study GR41675 with the U.S. FDA between 2019 and 2021. This SAP incorporates changes based on feedback received, as detailed in Appendix 3.

1.1 OBJECTIVES AND ENDPOINTS

1.1.1 Efficacy Objectives

1.1.1.1 Primary Efficacy Objectives

The primary efficacy objective for this study is to evaluate the superior efficacy of ranibizumab 100 mg/mL delivered via the PDS every 36 weeks (Q36W) compared with observation (comparator arm) on the basis of the following endpoint measured in the study eye:

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

1.1.1.2 Secondary Efficacy Objectives

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, 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 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 best-corrected visual acuity (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 1mm 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

*Note: CST is assessed by central reading center with boundaries of the inner limiting membrane (ILM) to Bruch's Membrane.

1.1.1.3 Exploratory Efficacy Objectives

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 (comparator arm) on the basis of the following endpoints:
  - Change from baseline in total area of ischemic non perfusion within the macula and ischemic non perfusion within the total retinal area 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

1.1.2 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 (AEs)
- Incidence and severity of non-ocular AEs
- Incidence, severity, and duration of adverse events of special interest (AESI), including ocular AESI
- Incidence, severity, and duration of ocular AESI during the postoperative period ($\leq$ 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 (ADEs)
- Incidence, causality, severity, and duration of anticipated serious ADEs (ASADEs).

The device safety objectives were added in version 2 of the Protocol and the ADEs are collected prospectively from the date of the new electronic Case Report Form (eCRF) go-live (June 14, 2021).

1.1.3 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 implant insertion and subsequent refill-exchange procedures in patients with DR on the basis of the following endpoints:

- Serum concentration of ranibizumab observed over time
- Additional estimated PK parameter values, including area under the concentration-time curve (AUC), maximum serum concentration (C_{max}), minimum serum concentration, and half-life ($t_{1/2}$) 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 concentration or PK parameters for ranibizumab delivered via the PDS and efficacy endpoints
- Relationship between serum concentration or PK parameters for ranibizumab delivered via the PDS and safety endpoints
- Measured aqueous humor concentrations of ranibizumab over time

1.1.4 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, neutralizing antibodies and efficacy, safety, or PK endpoints

1.1.5 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 AEs, 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

1.1.6 Patient Treatment Experience Objectives

The patient treatment experience objectives for this study are to evaluate patient treatment satisfaction on the basis of the following endpoint:

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

1.1.7 Exploratory Device and Procedure Experience Objective

The exploratory device and procedure experience objective for this study is to characterize the safety (as detailed in Section 5.6 of the Protocol) of the PDS devices and procedures on the basis of the following endpoints:

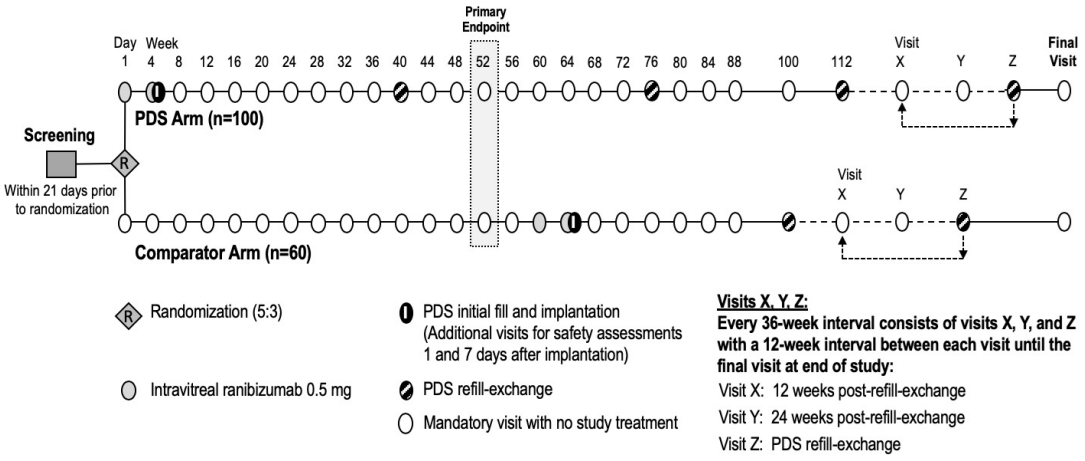
- Reported incidence of device deficiencies

The device deficiencies are collected prospectively from the date of the new eCRF go-live (June 14, 2021).

1.2 STUDY DESIGN

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 the PDS Q36W relative to the comparator arm. Approximately 160 patients with moderately severe or severe nonproliferative diabetic retinopathy (NPDR) (DRSS level 47 or 53) without CI-DME will be enrolled at approximately 100 investigational sites. For the study schema, see Figure 1.

Figure 1 Study Schema



PDS = Port Delivery System with ranibizumab

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 of the Protocol for inclusion and exclusion criteria). Patients who do not meet eligibility criteria (screen-failed patients) may be eligible to repeat screening up to two times if deemed appropriate by the Investigator.

After all eligibility requirements are confirmed, patients are to be randomly allocated in a 5:3 ratio so that approximately 100 patients receive the PDS implant filled with ranibizumab 100 mg/mL Q36W (PDS 100 mg/mL arm) and approximately 60 patients will be allocated to the comparator arm. On the day of a patient's randomization visit, ETDRS-DRSS level as assessed via color fundus photography (CFP) by central reading center and intraretinal or subretinal fluid status on SD-OCT as assessed by a central reading center will be confirmed. Randomization is 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. Randomization will be performed by the interactive web/mobile-based response system (IxRS)

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

Patients 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). Patients will receive PDS implant 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.

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 of the Protocol).

Patients randomized to the comparator arm will undergo study visits every 4 weeks (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 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.

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 following consultation, 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.

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 of the Protocol) 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 (see Section 4.3.2.3 of the Protocol).

In the PDS arm, all AEs will be collected after initiation of the first loading dose post-randomization.

In patients randomized to the comparator arm, prior to study drug initiation (either as a supplemental treatment prior to Week 60 or a loading dose), only the following AEs will be collected:

- Serious adverse events (SAEs) caused by a protocol-mandated intervention
- Severe acute respiratory coronavirus 2 (SARS-CoV-2)-related (due to viral infection or vaccine administration) AEs
- AEs leading to study discontinuation

After study drug initiation, all AEs will be collected.

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 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.

1.2.1 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 the following baseline factors:

- Baseline ETDRS-DRSS level (47 vs. 53) as assessed by a central reading center
- 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 optical coherence tomography [OCT] features) and/or storage.

1.2.2 Independent Review Facility (IRF)

The analyses of anatomical outcomes are based on central reading center assessments. The central reading centers will provide sites with the central reading center manuals 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 results will be obtained by trained site personnel at the study

sites and forwarded to the central reading center for independent, masked analysis and/or storage and will later be transferred to the Sponsor.

1.2.3 Data Monitoring

An independent Data Monitoring Committee (iDMC) will monitor safety in 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 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 conducts an unmasked interim safety review prior to the primary analysis. At the time of the primary analysis, four interim data reviews have been conducted by the iDMC; therefore, efficacy analyses will be performed at a significance level of 0.0496.

2. STATISTICAL HYPOTHESES

The primary efficacy endpoint is the proportion of patients with a ≥ 2-step improvement from baseline on the ETDRS-DRSS at Week 52. The study is designed to assess the superiority of ranibizumab 100 mg/mL delivered via the PDS Q36W compared with the comparator arm. The following null and alternative hypotheses will be tested at a two-sided $\alpha = 0.0496$ significance level:

The null hypothesis (H_o) is: $P_{PDS} - P_C = 0$

The alternative hypothesis (H_a) is: $P_{PDS} - P_C \neq 0$.

for which, P_{PDS} and P_C refer to proportion of patients who achieve a ≥ 2-step improvement from baseline on the ETDRS-DRSS for PDS arm and comparator arm, respectively.

For the key secondary endpoints numbers 2-5 and 7 listed in Section 2.1 that are based on rate, the null and alternative hypotheses are as follows:

The null hypothesis (H_o) is: $S_{PDS}(t) = S_C(t); for\ t\ in\ (0, 52\ Weeks)$.

The alternative hypothesis (H_a) is: $S_{PDS}(t) \neq S_C(t)$.

for which, $S_{PDS}(t)$ and $S_C(t)$ refer to the survival functions for PDS arm and comparator arm, respectively.

For the key secondary endpoint number 6 listed in Section 2.1 based on proportion, the null and alternative hypotheses will follow the same form as those of the primary endpoint.

2.1 MULTIPLICITY ADJUSTMENT

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. The primary and key secondary endpoints will be tested in the order shown below at a two-sided 0.0496 significance level, proceeding sequentially starting from the primary endpoint and testing each after achieving statistical significance on the previous endpoint. The sequence for endpoint testing will be the primary endpoint, followed by key secondary endpoints in the following manner:

1. Proportion of patients with a ≥ 2-step improvement from baseline on the ETDRS-DRSS at Week 52
2. Rate of patients developing a vision-threatening complication (defined as PDR or ASNV) or CI-DME (defined as CST ≥ 325 µm) through Week 52
3. Rate of patients developing PDR or ASNV through Week 52
4. Rate of patients developing CI-DME (defined as CST ≥ 325 µm) through Week 52
5. Rate of patients developing ≥ 2-step worsening from baseline on the ETDRS-DRSS through Week 52
6. Proportion of patients with ≥ 3-step improvement from baseline on the ETDRS-DRSS at Week 52
7. Rate of patients developing ≥ 3-step worsening from baseline on the ETDRS-DRSS through Week 52

3. SAMPLE SIZE DETERMINATION

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 randomized in a 5:3 ratio (n = 100 in the PDS arm and n = 60 in the comparator arm) will provide over 99% power to detect an absolute difference of 35% between arms in proportion of patients with a ≥ 2-step improvement

on ETDRS-DRSS at Week 52 under the following assumptions, and to provide adequate data for assessment of key secondary endpoints:

- 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 1.2.2)
- 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. However, at the time of closing to recruitment, the dropout rate was approximately 5%. It was determined that the sample size did not need to be further increased.

Detailed information regarding the sample size assumptions and calculation is provided in Appendix 1.

4. ANALYSIS SETS

The following populations are defined:

Table 1 Analysis Sets

Population	Definition
ITT Population	All patients who are randomized. Patients will be grouped according to treatment assigned at randomization.
Safety-Evaluable Population	All patients who receive any study treatment, and patients randomized to the comparator arm under observation, grouped according to treatment actually received prior to Week 52. In the PDS arm, the population includes all patients randomized to PDS receiving at least one loading dose, or any patient who received the PDS implant prior to Week 52. In the comparator arm, the population includes all patients randomized to the comparator arm who did not receive the PDS implant prior to Week 52.
PDS Safety Population	All patients who receive the PDS implant, including patients in the comparator arm who cross over to receive PDS at Week 64. Analyses on this population will only include data after first loading dose. Patients will be grouped according to treatment actually received prior to Week 52 (i.e. patients receiving PDS prior to Week 52 are grouped to the PDS arm, and patients receiving PDS after Week 52 are grouped to the comparator arm).
PDS PK Population	All patients who are randomized with at least one post implant PK sample available and who receive PDS at any time point, grouped according to treatment actually received prior to Week 52, and overall. Analysis is relative to time since implant insertion.

PDS PK Evaluable Population	All patients in the PDS PK Population excluding patients receiving intravitreal injections of ranibizumab in the study eye post PDS implant (including supplemental treatment) or patients with fellow eye ranibizumab after randomization, or bevacizumab treatment in either eye within 9 months prior to randomization or after randomization, or patients with septum dislodgment. Patients will be grouped according to treatment actually received prior to Week 52, and overall. Analysis is relative to time since implant insertion.
Aqueous Humor PK Evaluable Population	Subset of patients in the PDS PK Evaluable Population with at least one post implant aqueous humor PK sample. Patients will be grouped according to treatment actually received prior to Week 52,and overall.
Aqueous Humor Biomarker Evaluable Population	All patients who are randomized and receive study treatment, including patients randomized to the comparator arm under observation, and have at least one optional aqueous humor sample available. Patients who receive the PDS implant insertion at any other times besides Week 4, 8, 64 or 68 will be excluded from this population. Patients who receive PDS implant insertion at Week 4 or 8 will be grouped in the PDS arm. Patients who receive PDS implant insertion at Week 64 or 68 will be grouped in the comparator arm.

ITT = intent-to-treat; PDS = Port Delivery System with ranibizumab; PK = pharmacokinetic

5. STATISTICAL ANALYSES

The primary analysis will be performed when all patients have completed the Week 52 follow up, 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 (the end of which is determined 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.

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

5.1 GENERAL CONSIDERATION

Efficacy analyses will be based on the intent-to-treat (ITT) Population unless otherwise specified.

Descriptive summaries will include the mean, standard deviation (SD), median, and range for continuous variables, and counts and percentages for categorical variables. Missing data for descriptive summaries will not be imputed unless otherwise noted.

For all efficacy endpoints, comparative efficacy analyses will be performed during the comparator-controlled treatment period (randomization through Week 60). At the primary

analysis, only the efficacy assessments collected through Week 52 will be included in the comparative efficacy analyses and descriptive summaries. At the final (end of study) analysis only the efficacy assessments collected through Week 60 will be included in the comparative efficacy analyses and data collected through end of study will be included in summaries. For the safety summaries, only data reported through Week 52 will be included at the time of the primary analysis. At the time of the final analysis, safety summaries will include all safety data collected through end of study (see Section 5.6).

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 conducts an unmasked interim safety review prior to the primary analysis. At the time of the primary analysis, four interim data reviews have been conducted by the iDMC; therefore, efficacy analyses will be performed at a significance level of 0.0496. All CIs will be two-sided and at the 95.04% level.

The occurrence of each type of intercurrent event as defined in Section 5.3.1 will be summarized by treatment arm. Additionally, the occurrence of each type of intercurrent event due to coronavirus disease of 2019 (COVID-19) as defined in the supplementary analysis in Section 5.3.3 will be summarized by treatment arm.

Data collected in selected scheduled and unscheduled visits will be mapped to visits that appear in the schedule of assessments (see Appendix 1 of the Protocol) per the Protocol using the actual study day of assessment.

If there are multiple values in the same visit window, values closest to the scheduled study day will be used in the analysis. In the case of a tie, the worst-case value will be used. The value to be used in the analysis will be selected prior to the implementation of intercurrent event strategies. For patients in the ITT Population, the day of randomization will be designated Study Day 1. For the other populations, Day 1 is defined as the day that study treatment was first received (or day of randomization for comparator patients not receiving study treatment). Each assessment will be assigned a study day calculated as:

$$\textit{date of assessment - date of randomization or first study treatment} + 1$$

Baseline in the ITT Population is defined as the last non-missing value at or prior to Day 1. Typically, baseline will be the pre-dose Day 1 assessments, but may include screening results if the pre-dose Day 1 result is not available or missing, or if it is not collected at Day 1 according to the schedule of assessments.

In order to avoid potential confounding of the effect of explant procedure on efficacy analyses, for all efficacy summary tables analyses will include baseline data and all post-baseline data except for efficacy data collected within 37 days following explant procedure. In the case of an explant and re-implant occurring on the same day, efficacy data collected within 37 days following the explant and re-implant procedure will be excluded from all efficacy summary tables because of the expected temporary impact in the immediate post-operative period on these outcomes. These post explant exclusions of efficacy data will not apply to efficacy listings. Non-standard BCVA data (assessed by ETDRS BCVA testing with prior visit refraction, test performed by unmasked certified ETDRS BCVA assessor, or by uncertified experienced ETDRS BCVA assessor) will be excluded from the analysis and provided in a separate listing. ETDRS-DRSS scores of 90 represent that the image was not able to be graded so will be treated as missing and provided separately in a listing.

5.2 PATIENT DISPOSITION

Patient disposition (the number of patients randomized, treated, and completing the comparator-controlled treatment period ending at Week 52 (at the primary analysis) and at Week 60 (at the final analysis) and over the entire study) will be tabulated by treatment group in the ITT Population. Reasons for premature study treatment discontinuation and study discontinuation will be tabulated and a listing will be provided. Detailed, free text reasons for discontinuations due to physician decision, withdrawal by subject and 'other' reasons will be included in the listing.

5.3 PRIMARY EFFICACY ENDPOINT ANALYSIS

5.3.1 Definition of Primary Endpoint

The primary efficacy endpoint is the proportion of patients with a $\geq$ 2-step improvement from baseline on the ETDRS-DRSS at Week 52, where DRSS is assessed by a masked central reading center. The primary 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 who are naive to any treatment for DR in the study eye
- Variable: A $\geq$ 2-step improvement from baseline on the ETDRS-DRSS at Week 52
- Intercurrent events which occur prior to Week 52:
    a) Receiving any supplemental treatment: A composite variable strategy will be applied. Patients with this intercurrent event will be regarded as non-responders (i.e., they are regarded as not achieving 2-step improvement on the EDTRS-DRSS).
    b) Receiving any prohibited therapy (as defined in Section 4.4.2 of the Protocol, including prohibited therapy administered post study treatment discontinuation), or PRP in the study eye: A composite variable strategy will be applied where patients with this intercurrent event will be regarded as non-responders.

c) Discontinuing study treatment (PDS arm) or discontinuing study (comparator arm) due to an AE: A treatment policy strategy will be applied where all observed values will be used regardless of the occurrence of the intercurrent event.

d) Discontinuing study treatment (PDS arm) or discontinuing 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 proportion between PDS and comparator arms as assigned at randomization.

5.3.2 Main Analytical Approach for Primary Endpoint

The primary analysis will be performed using the Cochran–Mantel–Haenszel (CMH) test 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.

Patients receiving supplemental treatments, prohibited therapy, or PRP (intercurrent events a-b) 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 $\geq$ 2-step improvement from baseline.

ETDRS-DRSS level for patients who discontinue study treatment due to lack of efficacy or AE are unlikely to change in the absence of supplemental treatments, prohibited therapy or PRP and inclusion of data following treatment discontinuation is unlikely to bias results. Therefore, their assessments after the intercurrent events c-d (but before receiving supplemental treatment or prohibited therapy or PRP) will be included in the analyses. For these patients who discontinue study treatment due to lack of efficacy or AE who are also missing ETDRS-DRSS level at Week 52 the last observed ETDRS-DRSS level prior to Week 52 will be imputed.

If there are no post-baseline ETDRS-DRSS levels observed, the baseline level will be imputed (patient regarded as non-responder).

If a patient has more than one intercurrent event, the composite strategy in which patients are included as non-responders will take precedence over the treatment policy strategy.

For patients who do not have intercurrent events a-d and are missing ETDRS-DRSS level (including death) at Week 52, the outcome at Week 52 will be imputed using the last observed outcome prior to Week 52. Patients with missing baseline outcomes will be excluded from the analysis.

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

5.3.3 Supplementary Analyses for 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 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. The supplementary analysis will represent a conservative non-responder imputation strategy, which regards need for supplemental treatment, prohibited therapy, or PRP, or treatment discontinuation due to AE or lack of efficacy as a treatment failure regardless of their observed outcome at Week 52.

In the main analysis, after applying the intercurrent event strategies, missing data are imputed using the last observed ETDRS-DRSS level. In order to assess the impact of this imputation method, a supplementary analysis will be performed in which no missing data imputation is applied after the intercurrent event strategies have been implemented (completer 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 (e-h) the hypothetical strategy of censoring observations after the intercurrent event is used. Missing data are then imputed using the last observed outcome prior to the intercurrent event.

- Intercurrent events which occur prior to Week 52:
    a) Receiving any supplemental treatment: A composite variable strategy will be applied where patients will be regarded as non-responders (i.e., they are regarded as not achieving 2-step improvement on the EDTRS-DRSS).
    b) Receiving any prohibited therapy (as defined in Section 4.4.2 of the Protocol, including prohibited therapy administered post study treatment discontinuation) or PRP in the study eye not due to COVID-19: A composite variable strategy will be applied where patients will be regarded as non-responders.
    c) Discontinuing study treatment (PDS arm) or discontinuing study (comparator arm) due to an AE not due to COVID-19: A treatment policy strategy will be applied where all observed values will be used regardless of the occurrence of the intercurrent event.

d) Discontinuing study treatment (PDS arm) or discontinuing study (comparator arm) due to lack of efficacy per Investigator's judgment not due to COVID-19: A treatment policy strategy will be applied where all observed values will be used regardless of the occurrence of the intercurrent event.

e) Receiving any prohibited therapy (as defined in Section 4.4.2 of the Protocol, including prohibited therapy administered post study treatment discontinuation) or PRP in the study eye due to COVID-19: A hypothetical strategy will be applied where all values will be censored after the intercurrent event.

f) Discontinuing study treatment (PDS arm) or discontinuing study (comparator arm) due to COVID-19: A hypothetical strategy will be applied where all values will be censored after the intercurrent event.

g) Deviating from planned treatment administration schedule with potentially major impact on efficacy due to COVID-19: A hypothetical strategy will be applied where all values will be censored after the intercurrent event.

   - PDS Arm: Any missed implant or refill-exchange due to COVID-19, or missed 2 or more consecutive missed visits due to COVID-19 immediately followed by a supplemental treatment (reported as an intercurrent event at the second missed visit)
   - Comparator Arm: Two or more consecutive missed visits due to COVID-19 immediately followed by a supplemental treatment (reported as an intercurrent event at the second missed visit)

h) Death related to COVID-19: A hypothetical strategy will be applied, patient will be censored at the time of death.

The analysis methods for this supplementary analysis will be the same as those for the main analysis. Missing ETDRS-DRSS at Week 52 will be imputed using the last observed outcome prior to Week 52. Patients with missing baseline outcomes will be excluded from the analysis.

5.3.3.1 Subgroup Analyses for Primary Endpoint

The consistency of ≥ 2-step improvement from baseline on the ETDRS-DRSS results when comparing PDS and comparator arms will be investigated by estimating the treatment effect in subgroups based on age, (< 65 years, ≥ 65 years) sex (male, female), race (White, non-White), ethnicity (Hispanic, non-Hispanic), baseline ETDRS-DRSS (DRSS 47 vs DRSS 53), and glycosylated hemoglobin (HbA1c) (< 8.0%, ≥ 8.0%). Due to small numbers in some subgroups, the analyses will use Fisher's exact test with unadjusted proportions. The estimand and data handling rules follow those for the main analysis for the primary endpoint (see Section 5.3.2). Point estimates of treatment group differences in ≥ 2-step improvement with 95.04% CIs will be provided in forest plots.

5.4 SECONDARY EFFICACY ENDPOINTS ANALYSES

5.4.1 Key/Confirmatory Secondary Endpoints

5.4.1.1 Rate of Patients Developing a Vision Threatening Complication (Defined As PDR or ASNV) or CI-DME through Week 52

The rate of patients developing vision-threatening complications (defined as PDR or ASNV) or CI-DME (defined as CST ≥ 325 µm) through Week 52 will be estimated using the Kaplan-Meier method based on time from randomization to the time the first such event occurs. The estimand for the endpoint 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 naive to any treatment for DR in the study eye
- Variable: same as the endpoint
- Intercurrent events which occur prior to Week 52:
    a) Receiving any supplemental treatment: A composite variable strategy will be applied where the intercurrent event is considered to be an event in the analysis.
    b) Receiving any prohibited therapy or PRP, including prohibited therapy or PRP administered post study treatment discontinuation: A composite variable strategy will be applied where the intercurrent event is considered to be an event in the analysis.
    c) Discontinuing study treatment (PDS arm) or discontinuing study (comparator arm) due to an AE: A treatment policy strategy will be applied where all observed values will be used regardless of the occurrence of the intercurrent event.
    d) Discontinuing study treatment (PDS arm) or discontinuing 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: Event rates in PDS and comparator arms through Week 52, grouped as assigned at randomization, with p-value and hazard ratio (HR) for the difference.

The rate of patients developing vision-threatening complications or CI-DME through Week 52 will be estimated using the Kaplan-Meier method. A stratified log-rank test will be used for hypothesis testing comparing the PDS arm with the comparator arm with respect to time to the respective event. A Cox proportional hazards regression model will be used as a supportive analysis to estimate the HR and its 95.04% CI. The model will include treatment arm and will be stratified based on the stratified randomization factors as per IxRS. Patients who do not experience vision-threatening complications or CI-DME will be censored at the end of their time at risk (last visit at or before Week 52). The HR and 95.04% CI for the treatment effect (PDS vs. comparator) will be calculated based on the model.

5.4.1.2 Rate of Patients Developing PDR or ASNV through Week 52

The rate of patients developing PDR or ASNV through Week 52 will be analyzed using the same analysis method, estimand and data handling rules as Section 5.4.1.1.

5.4.1.3 Rate of Patients Developing CI-DME through Week 52

The rate of patients developing CI-DME (defined as CST ≥ 325 µm) through Week 52 will be analyzed using the same analysis method, estimand and data handling rules as Section 5.4.1.1.

5.4.1.4 Rate of Patients Developing ≥ 2-step Worsening from Baseline on the ETDRS-DRSS through Week 52

The rate of patients developing ≥ 2-step worsening from baseline on the ETDRS-DRSS through Week 52 will be analyzed using the same analysis method, estimand and data handling rules as Section 5.4.1.1.

5.4.1.5 Proportion of Patients with ≥ 3 Step Improvement from Baseline on the ETDRS DRSS at Week 52

The proportion of patients with a ≥ 3-step improvement from baseline on the ETDRS-DRSS at Week 52 will be analyzed using Fisher's exact test with unadjusted proportions. The estimand and data handling rules follow those for the main analysis for the primary endpoint (see Section 5.3).

5.4.1.6 Rate of Patients Developing ≥ 3-step Worsening from Baseline on the ETDRS-DRSS through Week 52

The rate of patients developing ≥ 3-step worsening from baseline on the ETDRS-DRSS through Week 52 will be analyzed using the same analysis method, estimand and data handling rules as Section 5.4.1.1.

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

A supplementary analysis will be performed where all intercurrent events from the key secondary endpoints with time-to-event outcomes (i.e. rate of patients developing) are treated as events. The supplementary analysis will represent a conservative non-responder imputation strategy, which regards need for supplemental treatment, prohibited therapy, or PRP, or treatment discontinuation due to AE or lack of efficacy as an event regardless of their observed outcome.

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 who are naive to any treatment for DR in the study eye
- Variable: Same as the endpoint
- Intercurrent events which 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 study/treatment due to lack of efficacy or AE prior to Week 52, where these intercurrent events will be treated as events in the analysis.

- Population-level summary: Event rates in PDS and comparator arms through Week 52, grouped as assigned at randomization, with p-value and hazard ratio (HR) for the difference.

The same analysis methods described in Section 5.4.1.1 will be used in this supplementary analysis.

5.4.1.8 Supplementary Analysis for the Time-to-Event Key Secondary Endpoints of Patients Developing a Vision Threatening Complication (Defined As PDR or ASNV) or CI-DME

An additional supplementary analysis will be performed for the key secondary endpoints of:

- Rate of patients developing a vision threatening complication (defined as PDR or ASNV) or CI-DME through Week 52
- Rate of patients developing a vision threatening complication (defined as PDR or ASNV) =through Week 52
- Rate of patients developing CI-DME through Week 52

The criteria for receiving supplemental treatment is the development of PDR, ASNV or CI-DME. In the main analysis, receipt of supplemental treatment is an intercurrent event and treated as event in the analysis. This supplementary analysis is included to assess the time to a vision threatening complication or time to CI-DME individually.

Intercurrent events of receipt of supplemental intravitreal ranibizumab 0.5 mg injection treatments, prohibited therapies or PRP will be treated using the hypothetical strategy in which all values will be censored after the intercurrent event.

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 who are naive to any treatment for DR in the study eye
- Variable: Same as the endpoint
- Intercurrent events which occur prior to Week 52:
    - Receiving any supplemental treatment: A hypothetical strategy will be applied where all values will be censored after the intercurrent event.
    - Receiving any prohibited therapy or PRP, including prohibited therapy or PRP administered post study treatment discontinuation: A hypothetical

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

- Discontinuing study treatment (PDS arm) or discontinuing study (comparator arm) due to an AE: A treatment policy strategy will be applied where all observed values will be used regardless of the occurrence of the intercurrent event.
- Discontinuing study treatment (PDS arm) or discontinuing 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: Event rates in PDS and comparator arms through Week 52, grouped as assigned at randomization, with p-value and hazard ratio (HR) for the difference.

The same analysis methods described in Section 5.4.1.1 will be used in this supplementary analysis.

5.4.2 Additional Secondary Efficacy Endpoints

5.4.2.1 Proportion of Patients with A ≥ 2-step Improvement from Baseline on the ETDRS-DRSS over Time

The proportion of patients with ≥ 2-step improvement from baseline on the ETDRS-DRSS over time will be analyzed using the analysis method, estimand and data handling rules following those for the main analysis for the primary endpoint (see Section 5.3) comparatively through Week 52 and with adjusted proportions descriptively through end of study.

5.4.2.2 Proportion of Patients with a ≥ 3-step Improvement from Baseline on the ETDRS-DRSS over Time

The proportion of patients with ≥ 3-step improvement from baseline on the ETDRS-DRSS over time will be analyzed using analysis method, estimand and data handling rules as Section 5.4.1.5 comparatively through Week 52, and descriptively through end of study.

5.4.2.3 Time to First Development of Either PDR, ASNV, or CI-DME

The time to first development of either PDR, ASNV, or CI-DME will be analyzed using the same analysis method, estimand and data handling rules as Section 5.4.1.1 comparatively through Week 60, and will be estimated using the Kaplan-Meier approach through end of study.

5.4.2.4 Time to First Development of PDR or ASNV

The time to first development of PDR or ASNV will be analyzed using the same analysis method, estimand and data handling rules as Section 5.4.1.1 comparatively through Week 60, and will be estimated using the Kaplan-Meier approach through end of study.

5.4.2.5 Time to First Development of CI-DME

The time to first development of CI-DME will be analyzed using the same analysis method, estimand and data handling rules as Section 5.4.1.1 comparatively through Week 60, and will be estimated using the Kaplan-Meier approach through end of study.

5.4.2.6 Time to First Development of a ≥ 2-step Worsening from Baseline on the ETDRS-DRSS

The time to first development of a ≥ 2-step worsening from baseline on the ETDRS DRSS will be analyzed using the same analysis method, estimand and data handling rules as Section 5.4.1.1 comparatively through Week 52, and will be estimated using the Kaplan-Meier approach through end of study.

5.4.2.7 Time to First Development of a ≥ 3-step Worsening from Baseline on the ETDRS-DRSS

The time to first development of a ≥ 3-step worsening from baseline on the ETDRS DRSS will be analyzed using the same analysis method, estimand and data handling rules as Section 5.4.1.1 comparatively through Week 52, and will be estimated using the Kaplan-Meier approach through end of study.

5.4.2.8 Change from Baseline in BCVA As Measured on the ETDRS Chart over Time

This endpoint will be summarized using descriptive statistics for each study visit based on all observed data through the end of the study. This endpoint will also be analyzed using the mixed-effect model for repeated measures (MMRM) comparatively through Week 52 and through Week 60, and will be summarized using adjusted mean changes from the MMRM model through the end of the study.

The estimand for the endpoint 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 naive to any treatment for DR in the study eye
- Variable: change from baseline in BCVA score over time
- Intercurrent events:
    - Receiving any supplemental treatment: A treatment policy strategy will be applied where all observed values will be used regardless of the occurrence of the intercurrent event.
    - Receiving any prohibited therapy or PRP regardless of study drug discontinuation status: A treatment policy strategy will be applied where all observed values will be used regardless of the occurrence of the intercurrent event.
    - Discontinuing study treatment (PDS arm) or discontinuing study (comparator arm) due to an AE: A treatment policy strategy will be

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

- Discontinuing study treatment (PDS arm) or discontinuing 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

All observed data will be included in the analysis regardless of whether or not a patient has experienced an intercurrent event. Missing data will be implicitly imputed by the MMRM model, assuming a missing-at-random (MAR) mechanism. The dependent variable in the MMRM model is the change from baseline in BCVA at post-baseline visits and the independent variables are the treatment group, time, treatment-by-time interaction, baseline BCVA letter 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, the following covariance structures will be implemented in order until convergence is achieved: first order antedependence, heterogeneous Toeplitz and first order autoregressive.

5.4.2.9 Proportion of Patients Who Lose < 15, < 10 and < 5 Letters in BCVA from Baseline over Time

The proportion of patients who lose < 15, < 10 and < 5 letters (defined as change from baseline > −15, > −10, > −5 letters respectively) in BCVA from baseline over time will be summarized comparatively through Week 52, and through Week 60, and descriptively through end of study. The analysis will use an unadjusted normal approximation for binomial proportions.

5.4.2.10 Proportion of Patients with a BCVA Score of 69 Letters (20/40 Approximate Snellen Equivalent) or Better over Time

The proportion of patients with a BCVA score of 69 letters (20/40 approximate Snellen equivalent) or better over time will be summarized comparatively through Week 52, and through Week 60, and descriptively through end of study. The analysis will use an unadjusted normal approximation for binomial proportions.

5.4.2.11 Change from Baseline in CST As Measured on SD-OCT over Time

The change from baseline in CST as measured on SD-OCT over time will be analyzed using the same methods described in Section 5.4.2.8, comparatively through Week 52, and through Week 60, and will be summarized using adjusted mean changes through end of study.

5.4.2.12 Change from Baseline in Total Macular Volume As Measured on SD-OCT over Time

The change from baseline in total macular volume as measured on SD-OCT over time is a continuous endpoint and will analyzed using the same methods described in Section 5.4.2.8, comparatively through Week 52, and through Week 60, and will be summarized using adjusted mean changes through end of study.

5.4.2.13 Proportion of Patients with Absence of Intraretinal Fluid, Subretinal Fluid or Both over Time

The proportion of patients with absence of intraretinal fluid, subretinal fluid and both intraretinal and subretinal fluid as assessed by SD-OCT (as measured in the central 1mm subfield) over time will be summarized comparatively through Week 52, and through Week 60, and descriptively through end of study. The analysis will use an unadjusted normal approximation for binomial proportions.

5.4.2.14 Proportion of Patients Who Do not Undergo Supplemental Treatment with Intravitreal Ranibizumab within Each Refill-exchange Interval

This endpoint will be summarized descriptively during the entire study period and between each refill-exchange period for patients in the Safety-Evaluable Population. In order to avoid bias, the proportion of patients who do not undergo supplemental treatment will be evaluated using only the patients who were able to be assessed for the need for supplemental treatment, that is, patients who have the implant insertion with at least one visit in between implant insertion and first refill-exchange (or target day of first refill-exchange); or between two planned refill-exchanges in patients who had a refill-exchange at the start of the interval. This is the subset of patients who are assessed for the need of supplemental treatment at least once within a given refill-exchange interval.

At the final analysis additional summaries will be provided in the PDS Safety Population.

5.4.2.15 Proportion of Patients Who Report Preferring PDS Treatment to Intravitreal Ranibizumab Treatment, As Measured by the PPPQ at Week 52

The analysis of this endpoint is described in Section 5.7.6.1.

5.5 EXPLORATORY EFFICACY ENDPOINTS ANALYSIS

5.5.1 Change from Baseline in Total Area of Ischemic Non Perfusion within the Macula and Ischemic Non Perfusion within the Total Retinal Area over Time

The change from baseline in total area of ischemic non perfusion within the macula and ischemic non perfusion within the total retinal area over time will be analyzed using the same methods described in Section 5.4.2.8, comparatively through Week 52, and through Week 60, and will be summarized using adjusted mean changes through end of study.

Descriptive summaries will also present mean changes in the fellow eye, as well as the subgroup of patients never having received treatment in the fellow eye. Summaries will be presented comparatively through Week 52 and through Week 60, and overall through end of study, conditional on the availability of data at the time of reporting.

5.5.2 Time to First Vitrectomy for Complications of PDR

The time to first vitrectomy for complications of PDR will be analyzed using the same methods as Section 5.4.1.1 comparatively through Week 52, comparatively through Week 60, and using the Kaplan-Meier approach through end of study.

5.5.3 Time to First PRP

The time to first PRP will be analyzed using the same methods as Section 5.4.1.1 comparatively through Week 52, comparatively through Week 60, and using the Kaplan-Meier approach through end of study.

5.5.4 Proportion of Patients That Receive Supplemental Intravitreal Ranibizumab 0.5 Mg Injection after PDS Implant Insertion and Number of Supplemental Treatments Patients Receive

The proportion of patients that receive supplemental intravitreal ranibizumab 0.5 mg injection after the PDS implant insertion in the PDS Safety Population and number of supplemental treatments patients receive will be summarized descriptively through Week 52 (at primary analysis) and through the end of study (at final analysis) and between each refill-exchange. This endpoint is the complement of the secondary endpoint in Section 5.4.2.14.

5.5.5 Proportion of Patients in the Comparator Arm That Receive a Supplemental Intravitreal Ranibizumab 0.5 Mg Injection and the Number of Supplemental Treatments Patients Receive Prior to Week 52

The proportion of patients in the comparator arm Safety-Evaluable Population that receive a supplemental intravitreal ranibizumab 0.5 mg injection and the number of intravitreal treatments patients receive will be summarized descriptively through Week 52 (at primary analysis). The proportion of patients that receive an intravitreal ranibizumab 0.5 mg injection will be evaluated using only the patients who were able to be assessed for the need for supplemental treatment (those who are followed up to at least Week 4).

5.5.6 Evaluate Advanced Analytics Tools for the Assessment of Clinically Relevant Features

This analysis is planned in an exploratory fashion as the technology is in the early stages of development. Standard imaging analysis routinely performed by central reading center expert graders will continue to support the secondary objectives and endpoints outlined in Section 5.4. The evaluation of OCT and CFP with advanced analytics tools, such as machine learning and deep learning methods, are ongoing and

may help establish potential clinical use of this technology in the optimization of disease screening and early diagnosis, as well as prediction and monitoring of disease progression and treatment response. The analysis plan and analysis results for the advanced analytics will not be included in this SAP or the clinical study report (CSR), but will be provided separately.

5.6 SAFETY ANALYSES

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

Safety data will be summarized for the Safety-Evaluable Population at the time of the primary analysis through Week 52 and for the PDS Safety Population through the end of the study at the time of the final analysis (see Section 4) unless otherwise specified.

Safety summaries and listings in the Safety-Evaluable Population and in the PDS Safety Population will include data collected on or after Study Day 1 and PDS Day 1 respectively, which are defined as follows:

Table 2 Planned Safety Analyses

Population	Group	Data to be included in the analysis
Safety-Evaluable Population	PDS arm	Day of 1st loading dose injection (Study Day 1) to Week 52 at the primary analysis
Safety-Evaluable Population	Comparator arm	Day of randomization (Study Day 1) to Week 52 at the primary analysis
PDS Safety Population	PDS arm	Day of 1st loading dose injection (PDS Day 1) through EOS at the final analysis
PDS Safety Population	Comparator arm	Day of 1st loading dose injection (PDS Day 1) (expected at the Week 60 visit) through EOS at the final analysis

CCOD = Clinical Cut-off date; EOS = End of Study; PDS =Port Delivery System with ranibizumab

For patients randomized to the comparator arm, only key safety events (SAEs from Protocol mandated interventions, SARS-CoV-2 related AEs, and AEs leading to study discontinuation, see Section 5.3.1 of the Protocol) will be collected until study treatment (first administration of intravitreal ranibizumab 0.5 mg either as a supplemental treatment or a loading dose) is initiated. Upon initiation of study treatment, all AEs will be reported until the patient's final study visit.

5.6.1 Extent of Exposure

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

schedule set in Table 2. Summaries will include the number of intravitreal injections prior to implant, and time to implant post randomization.

For the Safety-Evaluable Population PDS arm duration of treatment is the time from first study treatment (intravitreal ranibizumab injection as loading) to the earlier of:

- The date of treatment discontinuation or date of study termination
- The date of Week 52 visit.

For the PDS Safety Population, duration of treatment is the time from 1st loading dose injection to the earlier of:

- The date of treatment discontinuation or date of study termination
- The final study visit at final analysis.

5.6.2 Adverse Events

All verbatim AE terms will be mapped to MedDRA thesaurus terms, and AE severity will be graded according to the AE Severity Grading Scale (see Table 8 in Protocol).

For safety analyses, unless otherwise specified, only treatment-emergent AEs will be included in the analyses. Treatment-emergent AEs will be defined as any new AE reported or any worsening of an existing condition on or after Study Day 1 or PDS Day 1 per Table 2 through the completion of the study or until a patient discontinues prematurely. AEs with missing onset date will be considered to be treatment-emergent. AEs with partially missing onset date will also be included as treatment-emergent when the month (if it was recorded) and the year occur on or later than the month and year of the study treatment start date.

Due to limited data collection for the comparator patients before their start of ranibizumab treatment, frequency tables, including patient incidence rates by treatment group, will be provided in the Safety-Evaluable Population grouped according to treatment actually received prior to Week 52 only for the events listed below:

- AEs leading to study discontinuation

In addition, SARS-CoV 2 related AEs will be provided in a listing by treatment group.

Frequency tables, including patient incidence rates by treatment actually received prior to Week 52 will be provided in the Safety-Evaluable Population, and in the overall PDS Safety Population from day of 1st loading dose injection for the events listed below:

- Ocular AEs and SAEs
- Non-ocular AEs and SAEs
- AESI defined as follows:
    - An AE considered to be sight-threatening (see Section 5.2.3 of the Protocol)

    - Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.6 of the Protocol)
    - Suspected transmission of an infectious agent by the study drug
    - Ocular AESI:
        - Vitreous hemorrhage
        - Endophthalmitis
        - Retinal detachment
        - Conjunctival retraction
        - Conjunctival erosion
        - Conjunctival bleb or conjunctival filtering bleb leak
        - Hyphema
        - Cataract
        - Device dislocation
- AEs leading to discontinuation of study treatment
- Treatment, device or procedure related Ocular AEs and SAEs as determined by the Investigator
- Anti-Platelet Trialists Collaboration (APTC) Events defined as:
    - Non-fatal stroke AEs defined by terms from the conditions associated with central nervous system haemorrhages and cerebrovascular accidents Standardized MedDRA Query (SMQ) (Narrow), ischemic cerebrovascular conditions SMQ (Narrow), and hemorrhagic cerebrovascular conditions SMQ (Narrow) or
    - Non-fatal myocardial infarction AEs defined by terms from the myocardial infarction SMQ (Narrow) or
    - Vascular death (including deaths of unknown cause)
- Deaths
- Intraocular inflammation (according to the Standardization of Uveitis Nomenclature (SUN) classification [Jabs et al. 2005]).

AEs will be tabulated by System Organ Class (SOC) and preferred term (PT), and summarized by AE onset day (pre-implant insertion, ≤ 37 days post-implant insertion, > 37 days post-implant insertion). Separate summaries will be prepared for ocular events in the study eye and fellow eye.

In addition, the following categories of events will be summarized for the overall PDS Safety Population by refill-exchange interval at the time of the final analysis to assess the temporal relationship of events to the refill-exchange procedure (post-operative

period (day of implant through Day 37), Day 38 through first refill-exchange, first refill-exchange through second refill-exchange, etc.):

- Ocular AEs and SAEs
- Ocular AESI and Serious Ocular AESI
- AEs leading to discontinuation of study treatment (also summarized in the Safety-Evaluable Population at Week 52) and AEs leading to explant
- Treatment or procedure related Ocular AEs and SAEs as determined by the Investigator
- AEs related to medical device deficiencies

Ocular AEs and SAEs within 9 days of intravitreal injection, implant or refill-exchange procedure will also be summarized separately. The 9-day cutoff was selected as patients return to the clinic at Day 7 (± 2 days) after implant surgery, and therefore the same window was selected for the evaluation of safety events after refill-exchanges and intravitreal injections.

Listings of AEs, SAEs, AESIs, AEs leading to early discontinuation of study treatment, AEs related to medical device deficiencies (see Section 5.4.4 of the Protocol), vitreous hemorrhage AEs, explantations, re-implantations and deaths will be provided with study day calculated both relative to randomization date and relative to the date of the PDS implant.

Intraocular inflammation is defined based on selected PTs according to the SUN as anterior uveitis (included iritis, iridocyclitis, anterior cyclitis, anterior chamber cell, flare, and inflammation); intermediate uveitis (included pars planitis, posterior cyclitis, hyalitis, vitritis, vitreous haze); posterior uveitis (included choroiditis, chorioretinitis, retinochoroiditis, retinitis, neuroretinitis, retinal vasculitis); and panuveitis (endopththalmitis); and events which were not otherwise specified (included eye inflammation, uveitis, post procedural inflammation, incision site inflammation, inflammation of wound, ocular vasculitis).

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

5.6.2.1 Adverse Device Effects

The prospective collection of device specific ADEs or procedure specific ADEs was added to the study on 14 June 2021, 10 months after the first patient received the PDS implant in the study. No device or procedure specific ADE data prior to 14 June 2021 was collected in the EDC. Summaries of device or procedure specific ADEs include patients who received the implant after the initiation of collection of device deficiencies

on June 14, 2021. ADEs collected prior to 14 June 2021 with unspecified relation to device or procedure are reported in summaries of treatment, device, or procedure related AEs. All reported ADEs are included in the listings with suspected causality or relation to device or procedure. ADEs will be summarized in the PDS Safety Population only at the time of the primary analysis and at the final analysis.

Frequency and number of ADEs (see Section 5.4.4 of the Protocol) and serious ADEs ([SADEs] anticipated and unanticipated) will be tabulated by SOC and PT, and summarized by AE onset day (≤ 37 days post-implant insertion, > 37 days post-implant insertion) in the PDS Safety Population, through Week 52 at primary analysis and EOS at final analysis.

ADEs leading to explantation and discontinuation of study, and incidence, severity and duration of SADEs during the post-operative period will be included in listings.

ADEs as assessed by Investigator and as assessed by Sponsor will be summarized by the worst case assessment of suspectedness and seriousness.

ADEs 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 provided in a listing as these are not study subjects and do not belong to the PDS Safety Population.

5.6.2.2 Additional Safety Analyses Performed for COVID-19

Based on the first reports of COVID-19 infection globally, the Sponsor determined that the window for all analyses of COVID-19 associated events would start from 01 December 2019.

Following the MedDRA 23.1 release, a COVID-19 SMQ (narrow) is now available. This SMQ includes 18 terms relevant to COVID-19 infection (see Table 3), and these terms will be used to assess the impact of COVID-19. Patients with AEs from this COVID-19 SMQ (narrow) will be considered to have a confirmed or suspected COVID-19 infection.

A listing or table of confirmed and suspected COVID-19 AEs will be produced from the patients identified from the search as having confirmed or suspected COVID-19 infection (Table 3).

Table 3 Roche COVID-19 SMQ (narrow) Preferred Terms for all Cases (Confirmed and Suspected)

Asymptomatic COVID-19
Breakthrough COVID-19
Congenital COVID-19
Coronavirus infection
Coronavirus pneumonia
Coronavirus test positive
COVID-19
COVID-19 immunisation
COVID-19 pneumonia
COVID-19 prophylaxis
COVID-19 treatment
Exposure to SARS-CoV-2
Multisystem inflammatory syndrome
Multisystem inflammatory syndrome in adults
Multisystem inflammatory syndrome in children
Occupational exposure to SARS-CoV-2
Post-acute COVID-19 syndrome
SARS-CoV-2 antibody test positive
SARS-CoV-2 carrier
SARS-CoV-2 RNA decreased
SARS-CoV-2 RNA fluctuation
SARS-CoV-2 RNA increased
SARS-CoV-2 sepsis
SARS-CoV-2 test false negative
SARS-CoV-2 test positive
SARS-CoV-2 viraemia
Suspected COVID-19
Thrombosis with thrombocytopenia syndrome
Vaccine derived SARS-CoV-2 infection

COVID-19 = coronavirus disease-2019; SARS-CoV-2 = severe acute respiratory coronavirus 2; SMQ = standardized MedDRA query.

In addition to presenting the suspected/confirmed COVID-19 infections, the Sponsor developed a broad search strategy for AEs associated with COVID-19 infection to further evaluate the confirmed events of COVID-19 and reported AEs that could be considered complications of the disease. This search strategy includes both the AEs of a confirmed or suspected COVID-19 infection (PTs in Table 3) and any AEs considered associated with COVID-19 (temporally reported around PTs in Table 4). As causality to COVID-19 was not collected on the standard eCRF, the Sponsor identified associated AEs as those reported ≤ 7 days before and ≤ 30 days after any reported AE suggesting a confirmed COVID-19 infection (PTs listed in Table 4). The COVID-19 associated AEs for patients with confirmed COVID-19 infection will be provided in a summary table or a listing.

Table 4 Roche COVID-19 SMQ (narrow) Preferred Terms for Confirmed Cases

Coronavirus infection
Coronavirus test positive
COVID-19
COVID-19 pneumonia
SARS-CoV-2 test positive
SARS-CoV-2 sepsis
SARS-CoV-2 viraemia
COVID-19 treatment
Multisystem inflammatory syndrome in children

COVID-19 = coronavirus disease-2019; SARS-CoV-2 = severe acute respiratory coronavirus 2; SMQ = standardized MedDRA query.

5.6.3 Device Deficiencies

The prospective collection of device deficiencies was added to the study on 14th June 2021, 10 months after the first patient received the PDS implant in the study. No device deficiency data prior to 14 June 2021 was collected in the EDC.

A listing of device deficiencies including the kind of device (implant, insertion tool, initial fill needle, refill needle, explant tool), whether the deficiency could have led to an SAE or posed a serious health threat as determined by the Investigator/ Sponsor and action taken with the device will be provided.

5.6.4 Laboratory Data

HbA1c will be summarized using descriptive statistics, including change from baseline summaries and a figure of change from baseline HbA1c over time by treatment group. With the exception of $HbA1_C$, laboratory data will be collected at baseline only (see Protocol Section 4.5.6). These data can be used for interpretation of some AEs, no general summary is planned.

5.6.5 Vital Signs

Vital signs, height and weight measurement will be recorded at screening and final visit only. These data can be used for interpretation of some AEs, no general summary is planned.

5.6.6 Ocular Assessments

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

- Intraocular pressure (IOP)

- Slit lamp examination
- Indirect ophthalmoscopy

Summaries of incidence of pre-dose IOP ≥ 30 mmHg by treatment group will be tabulated. The presence of intraocular inflammation and vitreous hemorrhage, as determined on slit lamp examination, will be tabulated by grade (according to grading scales for flares and cells in Protocol Appendix 7, and vitreous hemorrhage density and functional scales in Protocol Appendix 8). The presence of retinal break or detachment as determined from ophthalmoscopy will be tabulated.

5.7 OTHER ANALYSES

5.7.1 Summaries of Conduct of Study

Eligibility criteria deviations and other major Protocol deviations will be tabulated in the ITT Population and a listing will be provided. Summaries of duration of study follow-up will be provided for the ITT Population through Week 52 at the primary analysis and through end of study for the final analysis.

The impact of COVID-19 on data integrity will be assessed in terms of the following criteria:

- Discontinuing study treatment (PDS arm) or discontinuing study (comparator arm) due to COVID-19
- Missed treatments due to COVID-19 or related precautions
- Use of prohibited therapy due to COVID-19
- Missing ETDRS-DRSS assessments due to COVID-19 or related precautions
- Missing BCVA or BCVA not performed per Protocol due to COVID-19 or related precautions
- Major Protocol deviations associated with COVID-19 directly or indirectly
- Missed visits reported as due to COVID-19 or related precautions
- Early study discontinuation due to COVID-19
- Death due to COVID-19
- Confirmed or suspected cases of COVID-19 and AEs associated with COVID-19

Pre-treatment and concomitant systemic medications, ocular medications for the fellow eye, and ocular medications for the study eye will be summarized separately by treatment group in the in the Safety-Evaluable Population through Week 52 at the Primary Analysis and in the PDS Safety Population through End of Study. Listings of anti-VEGF treatment in the study eye following explantation and of anti-VEGF treatment in the fellow eye will be provided in the Safety-Evaluable Population.

5.7.2 Summaries of Treatment Group Comparability

Summaries by treatment arm for clinically important demographic and baseline characteristics will be provided in the ITT Population and in the PDS Safety Population. The variables will be summarized using means, SDs, medians, and ranges for continuous variables and proportions for categorical variables. The baseline summary will include:

- Age
- Sex
- Race
- Disease characteristics (duration of diabetes, type of diabetes, HbA1c, ETDRS-DRSS, BCVA, CST, etc.)

5.7.3 Pharmacokinetic Analyses

PK analyses will be performed in the PDS PK Population, PDS PK–Evaluable Population, and Aqueous Humor PK Evaluable Population (see Section 4).

Summaries of ranibizumab concentration data will be tabulated for each of the PK populations defined. Median serum ranibizumab concentration-versus-time data will be plotted in the PDS PK and PDS PK–Evaluable Populations. Summaries of ranibizumab concentration at the time of supplemental intravitreal ranibizumab treatment and subsequent treatment may be generated. Aqueous humor ranibizumab concentration data will be tabulated and plotted in the Aqueous Humor PK Evaluable Population.

Due to the sparse serum PK samples collected in the study, the AUC, C_{max} and t_{max} of ranibizumab cannot be obtained using observed data. The observed ranibizumab serum C_{min} by group will be tabulated and summarized (mean, SD, coefficient of variation, median, and minimum and maximum) by descriptive statistics. Between-patient variability will be evaluated.

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

5.7.4 Immunogenicity Analyses

The immunogenicity analysis population will include all patients with at least one ADA assessment. Baseline ADA prevalence will be estimated based on sample collected at the time of randomization; patients will be grouped according to treatment received or, if not treatment is received prior to study discontinuation, according to treatment assigned.

The immunogenicity incidence will be summarized according to treatment received prior to Week 52. ADA samples will be collected prior to dosing during the randomization visit and at Weeks 4, 8, 28, 52, 64, 76, and 112 in the PDS arm and during the randomization

visit and at Weeks 60, 64, 68, 88, and 100 in the comparator arm and at early termination or explant visit in both arms.

ADA incidence (number and percentage) will be summarized as follows in the PDS Population for the primary analysis at Week 52 and through the entire study at the final analysis:

– Pre-implant ADA incidence: at the last measure prior to implant (the reference visit)

– Post-implant ADA incidence: at any time after implant based on patients in the PDS Safety Population who have ADA samples at the reference visit and after implant:

a) PDS patients who were ADA negative at the reference visit and are with at least one positive result after implant. These patients are considered to have treatment-induced ADA responses.
b) PDS patients who were ADA positive at the reference visit and ADA titer increased after implant; in this case, the titer results of one or more samples collected after implant are at least 0.60 titer units greater than the titer result of the reference visit sample. These patients are considered to have treatment-enhanced ADA responses.

The combined rates described in (a) and (b) above will provide the incidence of patients positive for treatment-emergent ADAs. Patients are considered to be negative for Treatment-emergent ADAs if they are ADA negative at all timepoints after the reference visit. Patients are also considered to be Treatment unaffected for ADAs if they are ADA positive at the reference visit and (a) where all post-baseline titer results are less than 0.60 t.u. greater than the titer result of the reference visit, OR (b) where all post-baseline results are negative or missing. A listing of patients with positive serum antibodies to ranibizumab will be provided.

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

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

5.7.5 Biomarker Analyses

Biomarker analyses will be performed on the Aqueous Humor Biomarker Evaluable Population at the time of the Final Analysis. No biomarker analyses are planned at the Primary Analysis. Descriptive summaries of aqueous humor free VEGF concentration (original and log-transformed) and change in concentration from baseline will be tabulated and plotted by visit and by treatment arm.

The mean change from baseline in Free-VEGF log concentrations in the PDS arm at week W28 will be presented with a 95% CI.

The difference in the mean change from baseline in Free-VEGF fold change at W28/W24 between PDS and comparator arms respectively will be presented with a 95% CI.

Data after PDS implant from patients in the Aqueous Humor PK Population in patients with at least one post-implant Aqueous Humor PK sample will be summarized descriptively by treatment arm and overall.

Sensitivity analysis may be performed with the population that excludes patients who receive supplemental treatment.

Additional exploratory biomarker analyses to evaluate potential relationships between free VEGF, drug exposure, disease severity, and/or efficacy of the PDS will be performed, as applicable.

5.7.6 Patient Treatment Experience Assessment

The patients' perspective on their treatment experience will be captured through two questionnaires: the PPPQ and the RetTSQs.

5.7.6.1 PDS Patient Preference Questionnaire (PPPQ)

The PPPQ is a 3-item questionnaire that captures a patient's preference for treatment, the strength of their preference, and the reasons for their preference (Tschosik et al. 2019). The PPPQ will be administered only to patients who have experience with both PDS and intravitreal ranibizumab injections. The PPPQ specifically assesses patient preference for treatment and could demonstrate a benefit of PDS over intravitreal ranibizumab 0.5 mg due to less frequent treatments and the advantage of a refill-exchange over injection. However, due to the nature of the clinical trial, monthly visits are required so study patients will not experience the advantage of less frequent visits.

The endpoint relating to PPPQ is the:

- Proportion of patients who report preferring PDS treatment to intravitreal ranibizumab treatment, as measured by the PPPQ at Week 52.

This will be assessed by summarizing the following descriptively for strength of preference and reasons for preference:

- Proportion of patients who report preferring PDS treatment compared with intravitreal ranibizumab treatment, as measured by the PPPQ at Weeks 52 and 100 among patients in the PDS arm and at Week 112 among patients in the comparator arm who receive the PDS after completing the Week 64 visit

- Proportion of patients with bilateral disease (simultaneously receiving ranibizumab via study eye PDS implant and fellow eye intravitreal injection) who report preferring PDS treatment compared with intravitreal ranibizumab treatment, as measured by the PPPQ at Week 52 among patients in the PDS arm who receive PDS in their study eye and intravitreal ranibizumab in their fellow eye

5.7.6.2 Retinopathy Treatment Satisfaction Questionnaire, Status Version (RetTSQs)

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). The overall treatment satisfaction as measured by the RetTSQs total score at Week 52 will be summarized descriptively by treatment group as assigned at randomization.

5.8 INTERIM ANALYSES

Interim efficacy or futility analyses are not planned. Interim safety reviews will be performed by the iDCC periodically (approximately every 6 months) and will be reviewed by the iDMC (See Section 1.2.3 for details).

6. REFERENCES

Blinder KJ, Dugel PU, Chen S, et al. Anti-VEGF treatment of diabetic macular edema in clinical practice: effectiveness and patterns of use (ECHO Study Report 1). Clin Ophthalmol 2017;11:393–401.

Brose LS, Bradley C. Psychometric development of the retinopathy treatment satisfaction questionnaire (RetTSQ). Psychol Health Med. 2009;14(6):740-54.

Brown DM, Wykoff CC, Boyer D, et al. Evaluation of Intravitreal Aflibercept for the Treatment of Severe Nonproliferative Diabetic Retinopathy: Results From the PANORAMA Randomized Clinical Trial. JAMA Ophthalmol. 2021;139(9):946-55.

Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet 2010;376:124–36.

Cochran WG. Some methods for strengthening the common χ 2 tests. Biometrics. 1954;10(4):417-51.

Dugel PU, Layton A, Varma RB. Diabetic macular edema diagnosis and treatment in the real world: an analysis of medicare claims data (2008 to 2010). Ophthalmic Surg Lasers Imaging Retina 2016;47:258–67.

East 6 (2016). Statistical software for the design, simulation and monitoring clinical trials. Cytel Inc., Cambridge MA.

Eylea® (aflibercept injection) U.S. Package Insert, Regeneron Pharmaceuticals, Inc.

Flaxel CJ, Adelman RA, Bailey ST et al. Diabetic Retinopathy Preferred Practice Pattern®. Ophthalmology 2020; 127(1):P66-P145.

Fleiss JL. Statistical methods for rates and proportions. 2nd edn. Wiley, New York, 1981.

Fong DS, Luong TQ, Contreras R, et al. Treatment patterns and 2-year vision outcomes with bevacizumab in diabetic macular edema: an analysis from a large U.S. integrated health care system. Retina 2018;38:1830–8.

Gabrielian A, Hariprasad SM, Jager RD, et al. The utility of visual function questionnaire in the assessment of the impact of diabetic retinopathy on vision-related quality of life. Eye (Lond) 2010;24:29–35.

Holekamp NM, Campbell J, Almony A, et al. Vision outcomes following anti–vascular endothelial growth factor treatment of diabetic macular edema in clinical practice. Am J Ophthalmol 2018;191:83–91.

International Diabetes Federation. IDF diabetes atlas. 8th rev. ed. [resource on the Internet]. 2017 [cited: March 2018]. Available from: http://diabetesatlas.org/resources/2017-atlas.html.

Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140:509-516

Lee R, Wong TY, Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. Eye Vis. 2015;2(1):17.

Lucentis® (ranibizumab injection) Summary of Product Characteristics, Novartis Europharm Limited.

Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst.. 1959;22(4):719-48.

Mazhar K, Varma R, Choudhury F, et al. Severity of diabetic retinopathy and health-related quality of life: the Los Angeles Latino Eye Study. Ophthalmology 2011;118:649–55.

Mehrotra DV, Railkar R. Minimum risk weights for comparing treatments in stratified binomial trials. Stat Med. 2000;19(6):811-25.

Schmier JK, Covert DW, Matthews GP, et al. Impact of visual impairment on service and device use by individuals with diabetic retinopathy. Disabil Rehabil 2009;31:659–65.

SUSVIMO [package insert]. South San Francisco, CA: Genentech, Inc: 2021. https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=9c6d9e2a-9a77-4d11-b692-de87cfde3444&version=4

Tschosik E, Kapre A, Ferrara D, et al. Content validity of the Port Delivery System with ranibizumab Patient Preference Questionnaire. Invest Ophthalmol Vis Sci. 2019;60(9):5379.

Wecker T, Ehlken C, Bühler A, et al. Five-year visual acuity outcomes and injection patterns in patients with pro-re-nata treatments for AMD, DME, RVO and myopic CNV. Br J Ophthalmol 2017;101:353–59.

Weiss M, Sim DA, Herold T, et al. Compliance and adherence of patients with diabetic macular edema to intravitreal anti-vascular endothelial growth factor therapy in daily practice. Retina 2018;38:2293–300.

Westfall PH, Krishen A. Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. J Stat Plan Inference. 2001;99(1):25-40.

Willis JR, Doan QV, Gleeson M, et al. Vision-related functional burden of diabetic retinopathy across severity levels in the United States. JAMA Ophthalmol 2017;135:926–32.

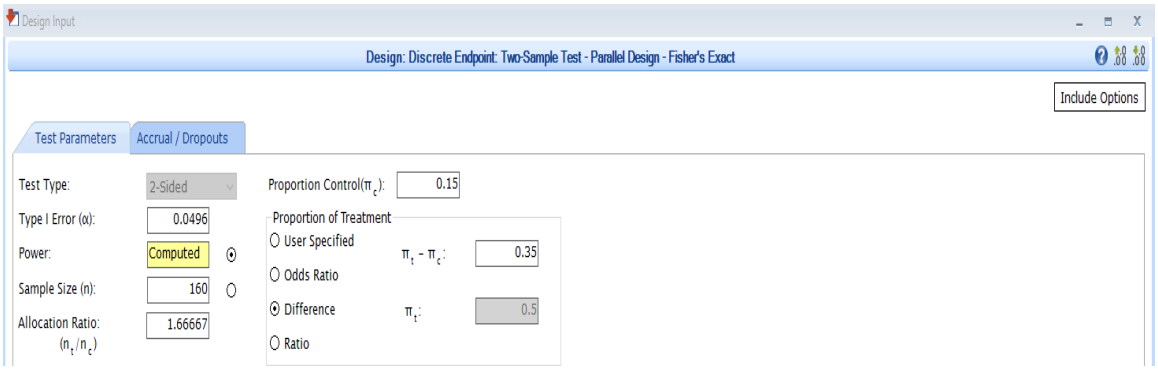
Yau JW, Rogers SL, Kawasaki R, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes care. 2012;35(3):556-64.

Appendix 1 Sample Size Calculation and Justification of Endpoints

The below parameters, formula, and screenshots are supplementary to Section 3.

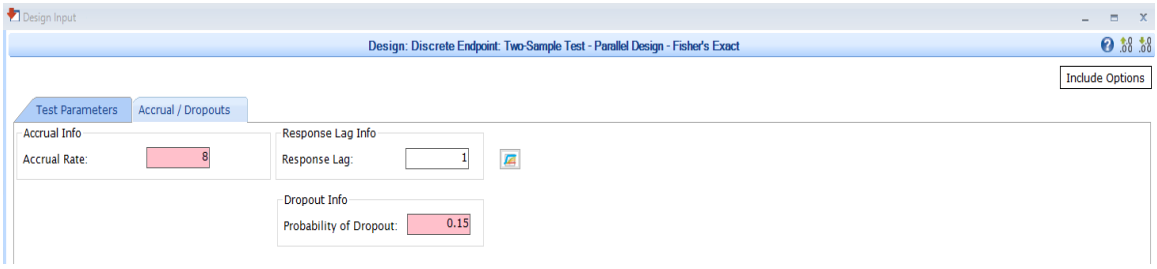
The power/ sample size was calculated using the East version 6.4.1 (2016) software as detailed in the screenshots below.

Figure 1 Screenshot 1 of Sample Size Calculation.



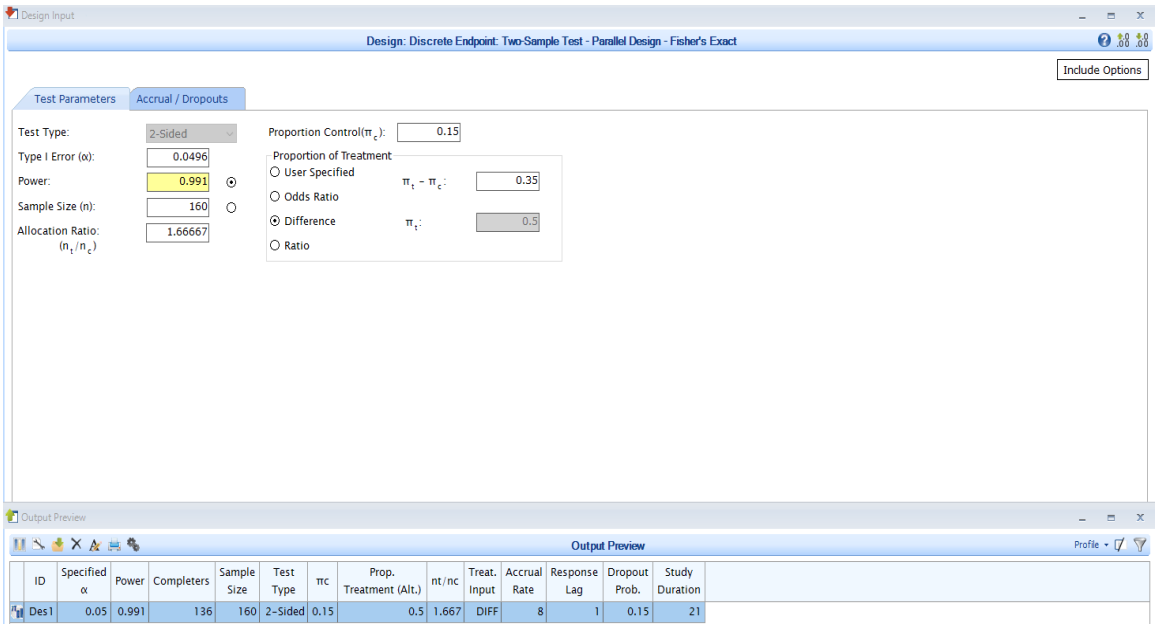
The above screenshot details the parameters for the Fisher's Exact Test power calculation including the type I error (α) two-sided, allocation ratio, proportion in control (comparator arm), proportion of treatment (PDS arm), and the sample size. Whilst CMH is used as the main analysis method, Fisher's Exact Test is expected to be less sensitive and a more conservative way to estimate the sample size.

Figure 2 Screenshot 2 of Sample Size Calculation.



The above screenshot details the input of the probability of dropout. The "Accrual Rate" and "Response Lag" do not impact the sample size calculation, and were only populated as they had to be non-zero to be able to edit the dropout information.

Figure 3 Screenshot 3 of Sample Size Calculation.



The above screenshot shows the full screenshot after hitting the “Compute” button, which resulted in the output table at the bottom of the screenshot. The resulting power is calculated as 99.1%.

Formula: The formula used by East to compute power and sample size for Fisher’s Exact Test are based on Fleiss (1981).

Let α be the maximum allowable type-1 error and $t_\alpha(m)$ be the smallest possible cut-off such that

$$\Pr(T \geq t_\alpha(m)|m, H_0) \leq \alpha\,. \tag{V.8}$$

The **conditional** power of Fisher's exact test is defined as

$$\Pr(T \geq t_\alpha(m)|m, H_1) = \sum_{\mathbf{x}\in\mathbf{\Gamma_m}(\mathbf{t}_\alpha(\mathbf{m}))} \left[\frac{Q_c Q_t}{\sum_{\mathbf{x}\in\mathbf{\Gamma_m}} Q_c Q_t}\right]\,. \tag{V.9}$$

where

$$Q_c = \binom{n_c}{x_c} \pi_c^{x_c}(1-\pi_c)^{n_c - x_c} \tag{V.10}$$

$$Q_t = \binom{n_t}{x_t} \pi_t^{x_t}(1-\pi_t)^{n_t - x_t} \tag{V.11}$$

Denote this two-sided conditional power by $(1-\beta(m))$. Then the two-sided **unconditional** power of Fisher's exact test is defined as

$$(1-\beta) = \sum_{m=0}^{N} (1-\beta(m))P(m) \tag{V.12}$$

where

$$P(m) = \Pr(x_c + x_t = m|H_1)\,, \tag{V.13}$$

is a convolution of two binomials under H_1. It is relatively straightforward to compute equation (V.12) as only 2×2 tables are involved.

Justification to Assumptions Used in Sample Size Estimation:

The proportion achieving a ≥ 2-step improvement on the ETDRS-DRSS in the comparator arm was selected based on the Eylea® U.S. Package Insert due to the similarities in study population for DR, and is estimated as 15%.

The proportion achieving a ≥ 2-step improvement on the ETDRS-DRSS in the PDS 100 mg/mL arm was selected based on considerations as to what would be considered a clinically meaningful improvement from the comparator, where a ≥ 35% absolute improvement was decided by Sponsor to be clinically relevant. Therefore, the proportion in the PDS 100 mg/mL arm was set to be 50%.

The above parameters result in an estimated power of 99.1% for the primary endpoint. In addition to the power of the primary endpoint comparison, the following factors are also taken into consideration in determining the sample size:

- Safety database (with support from safety data from GR40550 [Pagoda])
- Adequacy for key secondary endpoint comparisons

Justification to the Endpoints:

The primary endpoint was chosen as it is a well-established and validated outcome to objectively evaluate DR severity. Based on the Phase III, double-masked, randomized study of intravitreal aflibercept injection in patients with moderately severe to severe NPDR (Panorama; ClinicalTrials.gov Identifier: NCT02718326, Brown et al. 2021), an improvement in the ETDRS-DRSS appeared to be associated with a reduced rate of progression to vision-threatening complications. A 2-step or greater DR severity improvement on the ETDRS DRSS has been used to support the U.S. approval of ranibizumab and aflibercept for treatment of DR patients with DME and for treatment of DR (BLA 125156 / STN 106). This endpoint was also used to support the recent approval of Lucentis to treat patients with PDR in the EU (Lucentis SmPC), as well as the approval of Eylea to treat DR in the U.S. Taken together, the Sponsor considers this endpoint appropriate to demonstrate the superiority in clinical efficacy of PDS over observation. The key secondary endpoints were selected to capture clinically important events such as progression to e.g. PDR or to CI-DME (with loss of BCVA) or other complications.

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

PDR, ASNV, and CI-DME are sight-threatening complications associated with progression of DR and poor underlying disease control. Key secondary endpoints 1-4 and 6 are to assess whether PDS can reduce the risk of vision-threatening complications for individual event type or composite events through Week 52.

The 5th key secondary endpoint of ≥ 3-step improvement from baseline on the ETDRS DRSS at Week 52 provide useful information on the rates of a higher degree of improvement (≥ 3 steps) on DR severity.

Appendix 2 Diabetic Retinopathy Severity Score (DRSS) ETDRS Recode Values

DR severity scores (DRSS) are converted to the ETDRS recode values to assess DRSS step improvements as follows:

DRSS Values	ETDRS Recode Value (DRSS Step)
10, 12	1
14A, 14B, 14C, 14Z, 15, 20	2
35A, 35B, 35C, 35D, 35E, 35F	3
43A, 43B	4
47A, 47B, 47C, 47D	5
53A, 53B, 53C, 53D, 53E	6
61A, 61B	7
65A, 65B, 65C	8
71A, 71B, 71C, 71D	9
75	10
81	11
85A, 85B	12
90	Ungradable

Appendix 3 FDA Scientific Advice

The Sponsor sought feedback on the Statistical Analysis Plan of Study GR41675 with the U.S. Food and Drug Administration (FDA) between 2019 and 2021. The following is a summary of the key elements of the scientific advice that has been incorporated into this SAP, not a complete summary of all the advice received up to this point:

FDA feedback (January 16, 2020): written responses to the questions contained in December 4, 2019 Written Response Only Request		
Primary endpoint (Section 1.1.1)	The Agency agreed with the primary endpoint of the proportion of patients with ≥2 steps improvement from baseline on the ETDRS DRSS, but recommended for it to be at Week 52.	Primary endpoint was moved from Week 48 to Week 52
Analysis plan for the primary endpoint (Section 5.3)	The Agency agreed that the primary efficacy endpoint analysis was acceptable, but recommended a sensitivity analysis in which all intercurrent events are treated as treatment failures.	A supplementary analysis was added in which patients experiencing any intercurrent event prior to Week 52 are regarded as a non-responder (Section 5.3.3)
Analysis plan for the key secondary endpoints (Section 5.4.1)	The Agency agreed with the proposal for the Type I Error rate control for the key secondary endpoints. They recommended treating patients who have intercurrent events as having events in the time to event analyses.	Intercurrent events of receiving any supplemental or prohibited therapies are treated as having events rather than censored, but in order to reflect the main analysis for the study, intercurrent events of discontinuing due to AEs or lack of efficacy are treated using the treatment policy strategy. A supplementary analysis was added in which all intercurrent events are treated as an event.
FDA feedback: October 6, 2021 Teleconference (FDA Meeting Minutes dated November 1, 2021)		

Analysis plan for the primary endpoint (Section 5.3).	The Agency recommended treating patients experiencing an intercurrent event of receiving any supplemental or prohibited therapy as a non-responder (treatment failure) in the main analysis of the primary endpoint.	This was implemented (Section 5.3.2).
	The Agency confirmed that applying the treatment policy strategy to the intercurrent events of discontinuing study treatment due to AE or lack of efficacy is acceptable.	
	The Agency disagreed with treating COVID-19 events differently than other events.	Censoring of data post COVID-19 events was removed from the main analyses. A COVID-19 sensitivity analysis was included in which data post COVID-19 events are censored (Section 5.3.3).

Signature Page for Statistical Analysis Plan - GR41675 - Published
System identifier: RIM-CLIN-452974

Approval Task	[redacted] Scientific content approver 03-Oct-2022 12:53:59 GMT+0000