CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761197Orig1s000

DIVISION DIRECTOR, CROSS DISCIPLINE TEAM LEADER, AND MEDICAL OFFICER REVIEW

Medical Officer, CDTL, and Division Director Review of BLA 761197

Table 1. Administrative Application Information

Category	Application Information
Application type	BLA
Application number(s)	761197
Priority or standard	Priority review voucher redemption
Submit date(s)	4/23/2021
Received date(s)	4/23/2021
PDUFA goal date	10/23/2021
Division/office	Division of Ophthalmology (DO)
Review completion date	10/22/2021
Established/proper name	Ranibizumab injection
(Proposed) proprietary name	Susvimo
Pharmacologic class	Anti-Vascular Endothelial Growth Factor
Code name	NA
Applicant	Genentech
Dosage form(s)/formulation(s)	Intraocular solution, 100 mg/mL
Dosing regimen	2 mg every 24 weeks
Applicant proposed indication(s)/ population(s)	Treatment of Neovascular (Wet) Age Related Macular Degeneration
Proposed SNOMED indication	414173003 Exudative age-related macular degeneration (disorder)
Proposed Regulatory action	Approval
Approved dosage	0.5 mg qmonthly
Approved indication	Treatment of Neovascular (Wet) Age Related Macular Degeneration
Approved SNOMED term for indication (if applicable)	414173003 Exudative age-related macular degeneration (disorder)

Review Team

Discipline	Reviewer	Office/Division
Drug Substance/Drug Product/Immunogenicity	Amy Hsu	OBP/DBRR1
OBP Labeling	Koung Lee	OBP/IO
Drug Substance Microbiology/Facilities	Amy Devlin	OPMA/DBM
Drug Product Microbiology/Facilities	Jeanne Fringer	OPMA/DBM
Facilities Assessment Lead	Zhong Li	OPMA/DBM
Microbiology Quality Assessment Lead	Maxwell Van Tassell	OPMA/DBM
CMC RBPM	Anh-Thy Ly	OPRO/DRBPM1
Application Technical Lead	Kristen Nickens	OBP/DBRR1
OBP Review Chief	Qing Zhou	OBP/DBRR1
Device facility (port delivery system)	Alan Gion/Charles Chang	CDRH/OHT1
Device facility (initial and refill needle)	David Wolloscheck/Rumi Young	CDRH/OHT3
RPM	Lois Almoza/Diana Willard	ORO/DROSM
Signatory Authority	Wiley Chambers	OSM/DO
Cross-disciplinary Team Lead	William Boyd	OSM/DO
Clinical Reviewer	Wiley Chambers	OSM/DO
Nonclinical	Maria Rivera	ORDPURM/DPTRDPURM
Clinical Pharmacology	Amit Somani	OCP/DIIP
Biostatistics	Elena Rantou	OB/DBIV
OSE/DMEPA	Valerie Vaughan/Nasim Roosta	OMEPRM/DMEPAI
OPDP	Carrie Newcomer/Jim Dvorsky	OPDP
OSE/DPV	Rachna Kapoor/Ronald Wassel	OSE/OPE/DPVII
OSE/DEPI	Natasha Pratt/Mingfeng Zhang	OSE/OPE/DEPII

Contents

I. Executive Summary

Summary of Regulatory Action

BLA 761196, ranibizumab for the treatment of neovascular age related macular degeneration is recommended for approval. The Ladder and Archway clinical trials are adequate and well controlled trials which demonstrate the efficacy and relative safety of ranibizumab delivered by a port delivery system in the treatment of neovascular age related macular degeneration. While the efficacy of port delivery system using a ranibizumab solution of 100 mg/mL is equivalent to monthly intravitreal administrations of 0.5 mg, the risk of endophthalmitis is significantly increased. The significant improvement in visual acuity balanced against overall risk of endophthalmitis provides a positive benefit to risk ratio for most patients. The increased risk in endophthalmitis will be conveyed in a black box warning in the labeling.

Benefit-Risk Assessment

2.1 Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Neovascular age related macular degeneration (nAMD) if untreated will lead to visual loss.	Treatment is needed to prevent visual loss.
Current Treatment Options	Lucentis (ranibizumab injection), Eylea (aflibercept), Beovue (brolucizumab), Macugen (pegaptanib sodium injection) and Visudyne (verteporfin for injection) are all approved for the treatment of nAMD. Avastin (bevacizumab) is used off-label to treat nAMD.	The approved products are all safe and effective treatments for nAMD. With the exception of Visudyne, all treatment options require intravitreal injections every 1 to 3 months.
Benefit	Susvimo using a port delivery system in the vitreous was demonstrated to be equivalent to Lucentis in its ability to maintain visual acuity over a 40 week period.	The approved products reduce the risk of visual loss in patients with nAMD.
Risk and Risk Management	The drug substance is the same for Lucentis and Susvimo. Susvimo is associated with additional risks due to a foregin body inserted through the sclera and into the vitreous, which is likely the cause of the higher endophthalmitis rate. Susvimo is likely to be associated with higher doses of the drug substance in the anterior chamber.	While the risks associated with the drug substance are the same between Lucentis and Susvimo, the presence of a foreign body through the sclera and into the vitreous has the potential to allow microorganisms to enter the vitreous and cause endophthalmitis. A higher risk of endophthalmitis has been observed with this product compared to currently approved products. It is not known if there are risks associated with higher sustained doses of the drug substance in the anterior chamber.

2.2 Conclusions Regarding Benefit-Risk

The Ladder and Archway clinical trials are adequate and well controlled trials which demonstrate the efficacy and relative safety of ranibizumab delivered by a port delivery system (PDS) in the treatment of neovascular age related macular degeneration. While the efficacy of port delivery system using a ranibizumab solution of 100 mg/mL is equivalent to monthly intravitreal administrations of 0.5 mg, the risk of endophthalmitis is significantly increased. The decreased frequency of injections, each with an associated low risk of endophthalmitis, does not appear to completely offset the overall increased rate of endophthalmitis using the port delivery system. The significant improvement in visual acuity using either monthly administration or six month refilling of the port delivery system outweighs the overall low risk of endophthalmitis, but clear warning needs to be provided to patients and physicians. This benefit versus risk provides a positive benefit to risk ratio for most patients. The increased risk in endophthalmitis will be conveyed in a black box warning in the labeling.

II. Interdisciplinary Assessment

Introduction

Ranibizumab injection, given as doses of either (b) (4) 0.5mg or 2mg monthly has demonstrated safety and efficacy in treating neovascular age related macular degeneration.

3.1 Review Issue List

Key Review Issues Relevant to Evaluation of Benefit

Demonstration of efficacy

Efficacy in the treatment of neovascular age related macular degeneration was demonstrated in two clinical trials, Archway and Ladder. The Archway clinical trial demonstrated the non-inferiority of 100mg/mL in the port delivery system compared to monthly intravitreal injections of 0.5 mg. The Ladder clinical trial, while it was underpowered to demonstrate non-inferiority of 100mg/mL compared to monthly intravitreal injections did demonstrate the superiority of 100mg/mL compared to 10mg/mL.

Key Review Issues Relevant to Evaluation of Risk

Risk of Endophthalmitis

The risk of developing endophthalmitis is significantly higher (3x) in patients receiving the port delivery system (PDS) than in patients receiving monthly intravitreal injections during the controlled portion of the clinical trials. A total of 11 individuals had one or more episodes of endophthalmitis out of the 555 patients enrolled in the Archway trial, Ladder trial or their extensions. Only one patient out of approximately 200 patients treated with

multiple intravitreal injections developed endophthalmitis. Conjunctival erosion and/or regression may be a contributing factor in some of the cases of endophthalmitis.

Risk of Device Dislocation

As of 11 September 2020, 4 patients (4/443 [0.9%]) in the PDS population experienced a device dislocation AE in the study eye. All cases were considered severe and serious and had led to study treatment discontinuation. The size of the incision was found to be associated with the risk of device dislocation. Additional instructions were added to address the size of the incision.

Risk of Corneal Endothelial Cell Loss

The port delivery system with 100 mg/mL of ranibizumab results in a higher sustained delivery of ranibizumab into the anterior chamber. The risk of this higher sustained level of ranibizumab in the anterior chamber on the corneal endothelial cells is not known. While there were only rare corneal adverse events in the clinical trials, a more complete assessment of the corneal endothelial cells should be conducted. The applicant has committed to conduct a post-marketing assessment of corneal endothelial cell density.

3.2 Approach to the Review

The potential safety and efficacy of this application was initially derived from the Lucentis application, BLA 125156. Clinical trials for up to two years with monthly doses of (b) (4) 0.5 and 2 mg have been administered. The current application presents an alternative formulation and dosing schedule of the same active ingredient. Two adequate and well controlled studies (Ladder and Archway) evaluating the safety and efficacy of Susvimo were conducted and have been reviewed.

Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for [Drug]

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Randomized[2]	Number of Centers and Countries
NCT03677934 Archway GR40548	Patients with neovascular age related macular degenerations	Control type: Active Randomization 3:2 ratio Blinding: Single masked Biomarkers: None Innovative design features: None	Drug: Ranibizumab Dosage: 100 mg/mL refillable q24 weeks vs 0.5 mg q monthly Duration: 96 weeks wk	Primary: Best corrected visual acuity	251 100 mg/mL 167 2 mg	90 sites
NCT02510794 Ladder GX28228	Patients with neovascular age related macular degeneration	Control type: Dose Ranging 10 mg/mL, 40 mg/mL, 100 mg/mL and 0.5 mg qmonthly Randomization:3:3:3:2	Implant with 10, 40, or 100 mg/mL	Primary: Time until a patient first required the implant refill according to protocol-defined refill criteria	58 10 mg/mL 62 40 mg/mL 59 100 mg/mL 41 2 mg	49 sites
NCT03683251	Long term extension of Archway and Ladder Trials	Control type: None Randomization: None Blinding: None Biomarkers: None Innovative design features: None			Up to 1000	

Source: Reviewer
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
[2] If no randomization, then replace with "Actual Enrolled"
Abbreviations: BID, twice daily; DB, double-blind; LTE, long-term extension study; MC, multi-center; N, number of subjects; OL, open-label; PC, placebo-controlled; PG, parallel group; R, randomized

4. Patient Experience Data

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		Section 8.2
☐	Patient-reported outcome	
☒	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

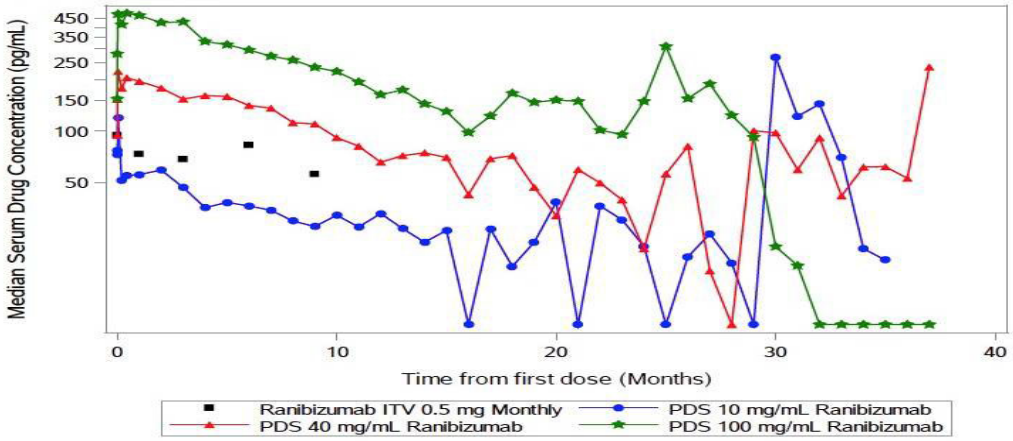
Table 5. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
Pharmacologic Activity	
Established pharmacologic class (EPC)	Vascular endothelial growth factor (VEGF) inhibitor SNOMED term:786911005 | Vascular endothelial growth factor receptor antagonist
Mechanism of action	Blocks receptor cites for vascular endothelial cell growth factor
QT prolongation	N/A – Minimal systemic availability
General Information	
Healthy subjects versus patients	Patients – Intravitreal products are not administered to healthy subjects.
Systemic exposure	See nested table below
Range of effective dosage(s) or exposure	0.5 mg – 2 mg intravitreally every month

	C_{max} (ng/mL)	T_{max} (day)	C_{min} [a] (ng/mL)	$AUC_{0\text{-}128\ Day}$ (day ng/mL)	$T_{½}$ [b] (day)
N	33	33	33	33	7
Mean (SD)	0.47 (0.16)	33.18 (37.82)	0.31 (0.08)	59.42 (21.11)	442.29 (276.92)
CV% Mean	34.0	114.0	24.5	35.5	62.6
Geometric Mean	0.45	11.66	0.31	53.05	376.54
CV% Geometric	32.6	543.4	24.9	69.9	67.0
Median (Min-Max)	0.45 (0.2-1.0)	27.11 (0.8-168.0)	0.31 (0.2-0.5)	57.25 (2.6-117.7)	406.12 (192.6-950.2)

[a] Same as C_{trough}
[b] Apparent terminal half-life

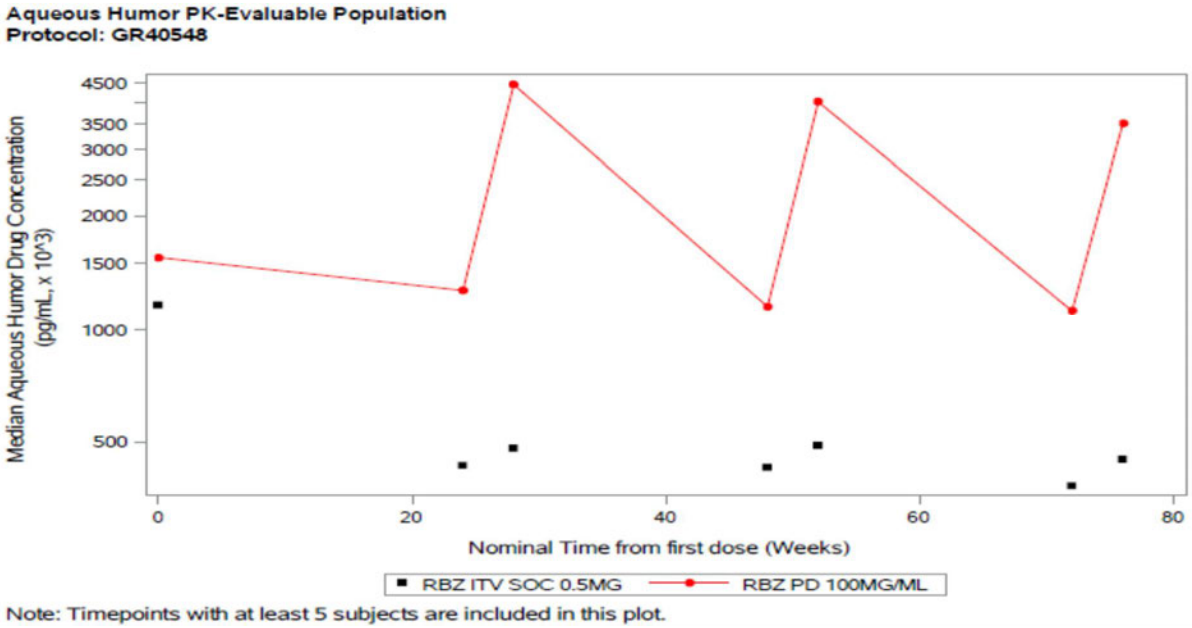
Median Serum Conc-Time Profile (Log-Scale) by Time on Study in Full PK Population, Study GX28228



Reviewer's Comments: *The systemic levels of ranibizumab with the Port Delivery are lower than the peaks that occur with monthly intravitreal dosing of ranibizumab and higher than the troughs that occur with monthly intravitreal dosing.*

Aqueous Humor Pharmacokinetics

Plot of Log-Scale Median of Aqueous Humor Ranibizumab Concentrations by Treatment Study GR40548



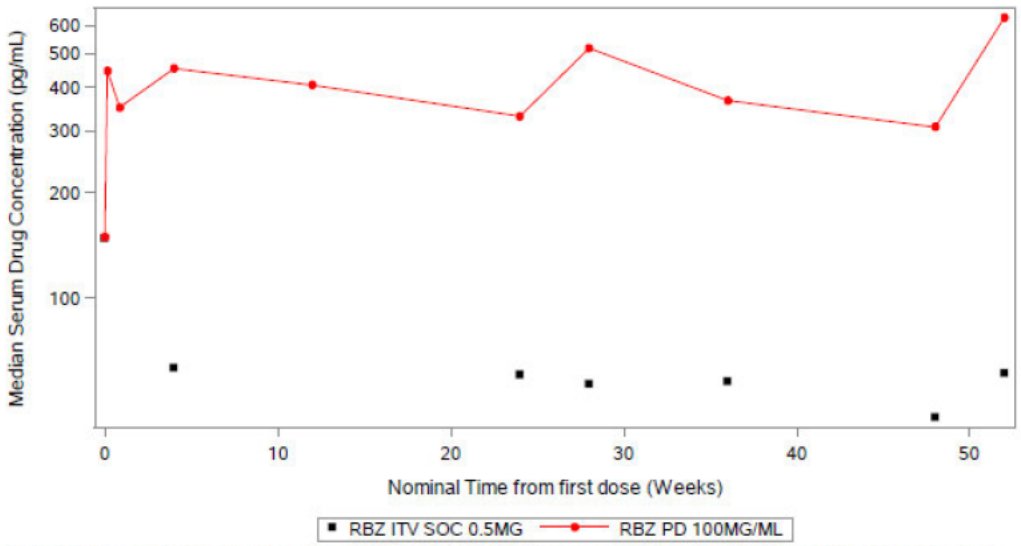
Note: Timepoints with at least 5 subjects are included in this plot.

		Geometric Mean (%CV) Ranibizumab Concentration in ng/mL					
Treatment Arm	Matrix	Randomization	Week 24 pre-refill-exchange	Week 28	Week 48 pre-refill-exchange	Week 52	Week 72 pre-refill-exchange
PDS 100 mg/mL (2 mg Q24W)	Aqueous Humor (N=40)	1140 (116)	1350 (81.4)	4530 (37.9)	1320 (67.2)	3050 (88.0)	671 (152)
	N	38	33	29	26	19	9
	Serum (N=40)	0.126 (113)	0.394 (70.2)	0.558 (40.3)	0.284 (89.5)	0.479 (47.2)	0.206 (92.1)
	N	40	37	29	29	18	15
		Randomization	Week 24 pre-dose	Week 28 pre-dose	Week 48 pre-dose	Week 52 pre-dose	Week 72 pre-dose
Intravitreal ranibizumab 0.5 mg Q4W	Aqueous Humor (N=46)	982 (111)	351 (218)	482 (225)	407 (225)	409 (240)	239 (265)
	N	37	37	35	36	35	20
	Serum (N=46)	0.117 (78.5)	0.0566 (188)	0.0581 (178)	0.0589 (149)	0.0562 (114)	0.0288 (140)
	N	46	45	35	38	34	20

Source: GR40548 Update CSR: Table 18

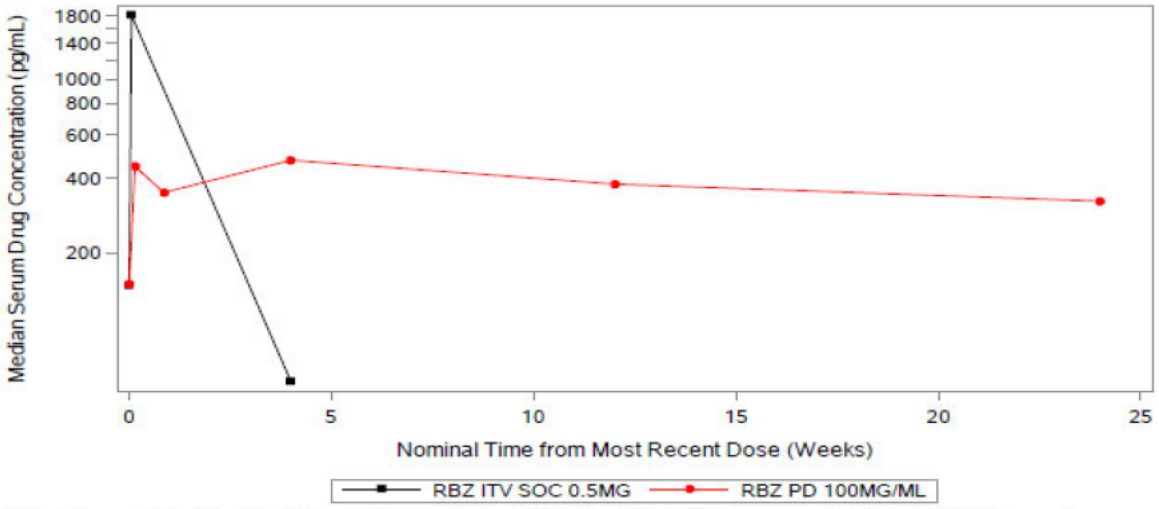
Reviewer's Comments: *Aqueous ranibizumab levels in the Port Delivery are significantly greater than with monthly dosing at trough. Peak aqueous levels with monthly dosing were not evaluated. The high sustained levels of ranibizumab in the aqueous suggest a need to evaluate the health of the corneal endothelial cells.*

Plot of Log-Scale Median Serum Ranibizumab Concentrations by Treatment for Subjects without Supplemental Treatment or Fellow Eye Treatment or Prior Bevacizumab Treatment
PK-Evaluable Population
Protocol: GR40548



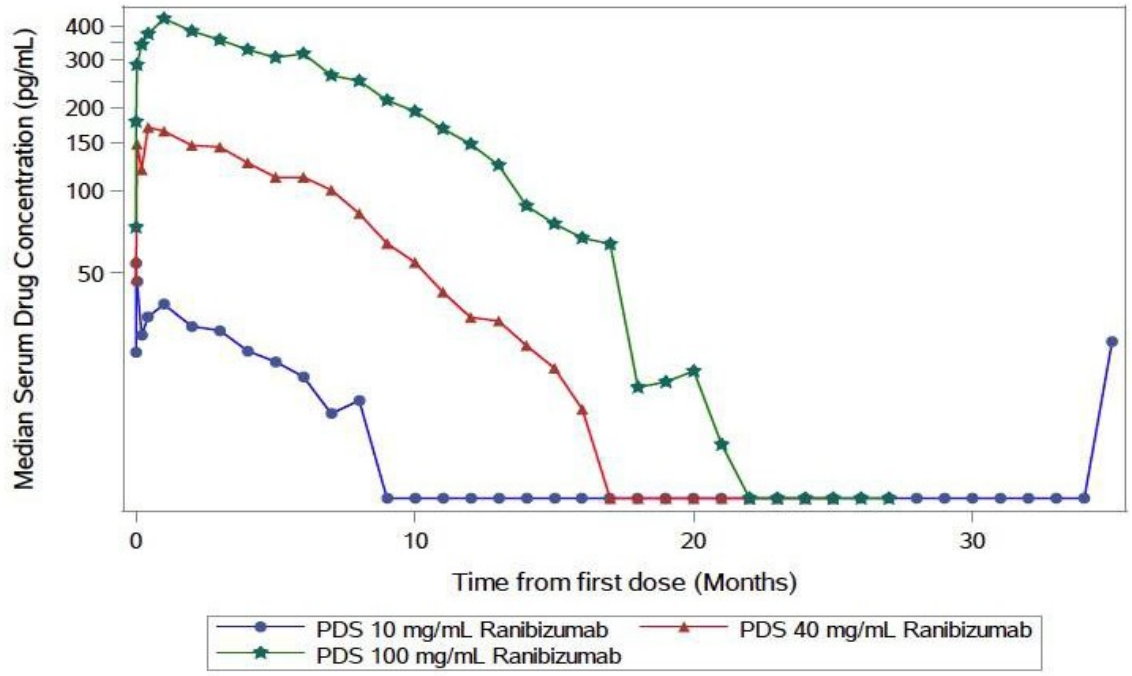
Note: Timepoints with at least 5 samples are included in this plot. The serum concentration (290000 pg/mL) on wk 48 for patient # (b) (6) was considered as an outlier (compared with the median serum concentration on wk 48 [~350 pg/mL]) and excluded from data summary.

Plot of Log-Scale Median Serum Ranibizumab Concentrations by Treatment for Subjects without Supplemental Treatment or Fellow Eye Treatment or Prior Bevacizumab Treatment
PK-Evaluable Population
Protocol: GR40548



Note: Timepoints with at least 5 samples are included in this plot. For the purpose of plotting, ITVPKO samples collected at 1-5 days postdose in the intravitreal arm was assigned as 3 days (or 0.4 week) postdose.
The serum concentration (290000 pg/mL) on wk 48 for patient # (b) (6) was considered as an outlier (compared with the median serum concentration on wk 48 [~350 pg/mL]) and excluded from data summary.

Median Serum Concentration-Time Profile (Log Scale) by Time Since Implantation up to First Refill in PK Population with Exclusions



Source: g_pkc1_median, t_pkc3

Pharmacokinetic Parameters [Geometric Mean (CV%)] in PK Population with Exclusions

Cohort	Refill Number	n[a]	Cmax (pg/mL)	T_{max}[b] (day)	C_{trough} (pg/mL)	AUC_{Last}[c] (ng•day/mL)	$t_{½}$[d] (day)
10 mg/mL	Implantation	16	105.52 (258.0)	11.45 (0–688.1)	14.96 (76.4)	5.89 (225.1)	168.20 (163.3)
	All refills	40	91.47 (187.2)	4.87 (0–688.1)	11.58 (65.7)	3.43 (176.8)	162.36 (129.3)
40 mg/mL	Implantation	24	220.87 (46.4)	12.87 (0–86.0)	61.64 (95.8)	28.39 (107.6)	88.30 (46.7)
	All refills	61	297.61 (115.2)	6.71 (0–91.1)	105.07 (77.4)	22.93 (96.9)	118.87 (76.2)
100 mg/mL	Implantation	27	1080.69 (272.5)	29.01 (0.8–180.3)	129.63 (149.2)	90.83 (64.7)	119.07 (128.4)
	All refills	70	1131.01 (256.6)	6.97 (0.8–180.3)	62.19 (345.2)	66.12 (71.4)	143.87 (171.4)

AUC_{Last}=area under the concentration-time curve from dosing (implant or refill) to last observation before next refill or exiting the study; C_{max}=maximum concentration; C_{trough}=concentration at trough, before next refill; CV=coefficient of variation;

Parameters are geometric means unless otherwise noted, with geometric mean CV% in parenthesis. This summary is for patients who did not have prior treatment with bevacizumab, did not have fellow eye treatment, and did not have supplemental intravitreal ranibizumab.

a For implantation n refers to number of patients; for all refills, n refers to number of refill cycles (implantation to first refill, first refill to second refill, etc.). The number of refill cycles per patient varies.
b Median (range) is reported.
c The interval between each refill cycle (implantation to first refill, first refill to second refill, etc.) is variable between patients.
d Apparent terminal half-life. Source: t_pkp2

6. Product (From Office of Biotechnology Products Reviews)

6.1 Composition of Ranibizumab PDS Drug Product

Ingredients	Nominal Amount per Vial	Concentration	Function	Specification
Ranibizumab	10 mg	100 mg/mL	Active ingredient	Section S.4.1 *Specification*
Histidine HCl	(b) (4) mg	(b) (4)	(b) (4)	
				(b) (4)
Sucrose	8.2 mg	240 mM	(b) (4)	USP-NF/Ph. Eur./JP
Polysorbate 20	0.01 mg	0.1 mg/mL		USP-NF/Ph. Eur./JPE
Water for Injection	(b) (4)	(b) (4)		USP-NF/Ph. Eur./JP

a (b) (4)

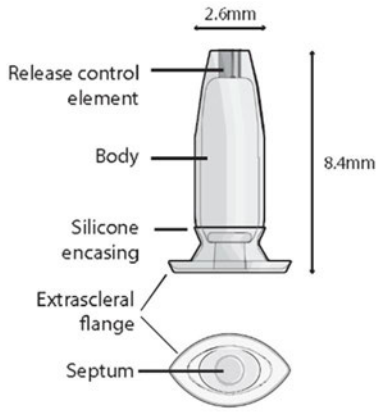
b (b) (4).

6.2 Drug Product Specification

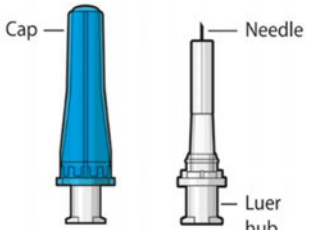
Test	Release	Stability Limit
Ph. Eur. Color Scale	not more colored than (b) (4)	not more colored tha (b) (4)
Clarity/Opalescence		
Ph. Eur. Opalescent Value (REF)	(b) (4)	(b) (4)
Visible Particles	(b) (4)	(b) (4)
Subvisible Particles		
Particles ≥ 10 µm per mL	max. (b) (4)	max. (b) (4)
Particles ≥ 25 µm per mL	max.	max.
Particles ≥ 50 µm per mL	max.	max.
pH	(b) (4)	
Osmolality	(b) (4) mOsm/kg	
Identity of Ranibizumab by CIEF	positive identity	
by Content of Protein (UV)	conforms	
Purity by SE-HPLC Main Peak	min. (b) (4) area%	min (b) (4) area%
Sum of HMW Forms	max. (b) (4) area%	max (b) (4) area%
Purity by IE-HPLC Main Peak	min. (b) (4) area%	min (b) (4) area%
Acidic Region	max. (b) (4) area%	max. (b) (4) area%
Purity by IE-HPLC Basic Region	max. area%	max. (b) (4) area%
Purity by NR-CE-SDS		
Sum of LMW Forms	---	max. (b) (4) %CPA
Content of Protein by UV	(b) (4) — (b) (4) mg/mL	---
Content of Polysorbate 20		
by HPLC-ELSD	min. (b) (4) mg/mL	min. (b) (4) mg/mL
Potency by Bioassay	(b) (4) — (b) (4) U/mg	(b) (4) — (b) (4) U/mg
Sterility Final Container	No growth	---
Bacterial Endotoxins	max. (b) (4) EU/mL	---
Container Closure Integrity		
by Dye Leak Test	---	no leakage detected

6.3 Device Constituents of PDS

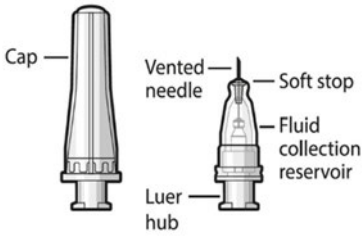
Implant



Initial Fill Needle

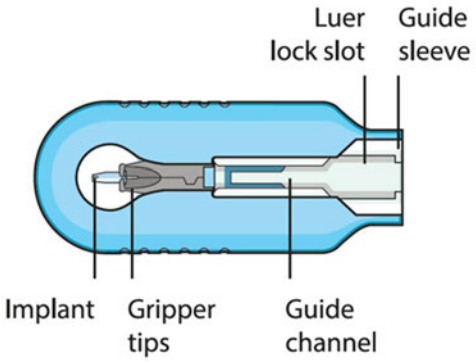


Refill Needle

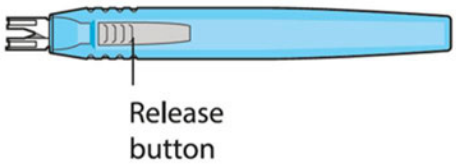


Insertion Tool Assembly

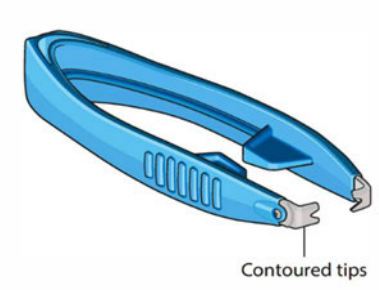
IT Carrier (with implant)



IT Handle



Explant Tool



The Office of Pharmaceutical Quality (OPQ), CDER, recommended approval of STN 761197 for Susvimo (ranibizumab injection) manufactured by Genentech, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Susvimo is well-controlled and leads to a product that is pure and potent. OPQ recommended that this product be approved for human use under conditions specified in the package insert. The OPQ recommendation takes into account the outcomes of the Office of Regulatory Affairs (ORA)-led CDRH recommended device facility inspections.

Manufacturing location:
- Drug Substance: Roche Singapore Technical Operations (RSTO) Pte. Ltd., 10 Tuas Bay Link, Singapore, Singapore (FEI: 3007164129)

- Drug Product: (b) (4)

- Co-packaging of Drug Product vial and Initial Fill Needle: Genentech, Inc., 4625 NE Brookwood Parkway, Hillsboro Technical Operations, OR 97124

- Device Manufacture of Individual Device Components: Philips-Medisize, LLC, 409 Technology Drive East, Menomonie, Wisconsin, 54751 (FEI :3002919960)

- Device Design Controls: Genentech, Inc., 1 DNA Way, South San Francisco, CA, 94080 (FEI:2917293)

Fill size and dosage form: 0.1 mL of 100 mg/ mL solution in a single-dose vial

Dating Period:
Drug Product: 24 months at 2-8°C, do not freeze, protected from light, do not shake
Drug Substance: (b) (4) months at (b) (4) C

For packaged products: Susvimo (ranibizumab) vial and initial fill needle kit; the expiration date for the co-package containing the initial fill needle and a ranibizumab vial shall be based on the earlier expiration date of the two components within. The co-packaged carton is labeled as follows: Refrigerate at 2°C to 8°C. Prior to use, the unopened vial may be kept at 9°C to 30°C for up to 24 hours. Do not freeze. Protect from light. Do not shake.
Susvimo Drug Product vial: 24 months: 2-8°C
Susvimo Initial Fill Needle: (b) (4) months (b) (4) °C

Stability protocol(s) in the license application have been approved for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.

Exempt from lot release: Yes, Exempted from lot release per FR 95-29960.

A claim of categorical exclusion from environmental assessment (EA) according to 21 CFR 25.15(d) was provided. The citation states that specifically, under 21 CFR Section

25.31(c), any action on an NDA, abbreviated application, application for marketing approval or a biologic product, or a supplement to such applications, or action on an OTC monograph, is categorically excluded and ordinarily does not require the preparation of an EA or statement for substances that occur naturally in the environment when the action does not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment. Genentech states that to their knowledge, no extraordinary circumstances exist that would significantly affect the quality of the human environment as a result of the proposed action. Therefore, a categorical exclusion from the requirement of an EA under 21 CFR 25.31(c) is applicable to Susvimo.

A Phase 4 (Post-Marketing) Commitment is included with this application. The commitment is to perform real-time Susvimo drug product commercial container closure system leachable studies using appropriate test methods to identify and quantify volatile organic compounds (VOC), semi-VOC, and non-VOC, and elemental impurities at regular intervals through the end of shelf-life. The leachables results will be updated annually in the BLA Annual Report. The final results of this study and the toxicological risk evaluation for the levels of leachates detected in the drug product will be provided in the final study report to the BLA.

7. Pharmacology/Toxicology

(from Pharmacology/Toxicology Review by María I. Rivera, PhD)

The pivotal nonclinical studies supporting this application included a 6-month ocular toxicity study in minipigs with the Port Delivery System **(**RPDS**)** refilled every month for a total of 7 ranibizumab doses, an ocular toxicity/tolerability studies of up to 6-month duration in rabbits with a scaled nonfunctional (no ranibizumab) implant, and a 61-day PK study in minipigs with RPDS administered 2 ranibizumab doses (Day 1 and one refill on Day 46). In rabbit studies of up to 2-month and 6-month duration with the RPDS implant alone (scaled one-third size, non-functional), the implant was well tolerated. The ocular findings were considered procedure related as they were comparable between implanted right eyes and sham surgery left eyes. The findings persisted generally up to 1 month after surgery, resolving with dissolution of the absorbable sutures in the conjunctiva.

The ocular toxicities observed in the minipig 6-month RPDS ocular toxicity study were consistent with an immune-mediated response to a foreign (humanized) protein, resulting in the early sacrifice of one animal (5 days after the 5th dose) with severe mixed cell pan-ophthalmitis. Transient inflammatory reactions and fibrosis around the implant were related to the implant itself, although the fibroplasia appeared to be exacerbated by ranibizumab. A NOAEL was not determined in the study. Immunogenicity in animals may or may not be predictive of a similar effect in humans. The evaluated RPDS dose of 2.1 mg in the minipig (0.7 mg/mL vitreous) provides a 1.4X ocular exposure margin for the 2.0 mg intended human dose (0.5 mg/mL vitreous), when considering a vitreous volume of 3 mL in the minipig and 4 mL in humans.

Although exposure margin is low, the following observations support there are no additional nonclinical concerns for the safety of ranibizumab administered through the RPDS:

- There is a long history of use with Lucentis® at an FDA approved dose of 0.5 mg/month (or 3 mg in 6 months) compared to a loading dose of 2 mg in the RPDS released over 6 months.
- In vitro release data showed lower cumulative ranibizumab release with the RPDS (1.3 mg ranibizumab over 24 weeks) compared to monthly dosing of Lucentis® (3.0 mg total ranibizumab from IVT Lucentis 0.5 mg in 6 months). In addition, the average daily release rate (18 μg/day initially) is only 4% the approved 0.5 mg monthly dose of Lucentis®) and decreases over time.
- Nonclinical PK data in minipigs supports ranibizumab ocular and/or systemic exposure observed with the implant is lower and/or comparable to that observed with IVT Lucentis® 0.5 mg.
- Comparative vitreous data is limited to one timepoint (2 weeks after implant refill). Ranibizumab concentrations in the vitreous were comparable to those observed after IVT injection (0.5 mg) at a similar timepoint (i.e., Days 12 and 18 postdose).

Serum data provides indirect information for implant release; serum concentrations with the implant were generally lower than those observed after IVT injection prior to the development of an immunogenic response on Day 15. After Day 15, serum concentrations in RPDS-treated animals increased but were generally within Cmax range observed with IVT injection. In the 61-day PK study in the minipig, the serum PK profile in animals with the RPDS was consistent with continuous release of ranibizumab from the implant. However, the serum concentrations appeared to exhibit a biphasic pattern; high concentrations at 6 hours post-dose, lower concentrations at 24 hours post-dose, and then, the serum concentrations were observed to rise over the next couple of weeks. The Applicant hypothesis is that the increase in ranibizumab serum exposure (after the initial decline) may be attributable to anti-therapeutic antibodies (ATAs) acting as carrier proteins for ranibizumab, thus decreasing ranibizumab clearance due to the addition of an Fc portion when ATAs are complexed with the drug. Interestingly, an opposite effect was observed in the 6-month ocular toxicity study in minipigs. The ATA response led to decreased serum concentrations with each monthly refill to levels below the lower limit of quantitation, with only one minipig having measurable levels at after the final refill (refill # 7). As noted by the Applicant, the variable impact of ATA across these studies may have been caused by the presence of both clearing ATAs and sustaining ATAs. Clearing ATAs have been noted to increase systemic clearance via reticuloendothelial system mediated recognition and removal of the ATA-drug complex, whereas sustaining ATAs have been noted to decrease systemic clearance via FcRn-mediated recirculation of the ATA-drug complex. Per information in Section 6.2 Immunogenicity of the proposed label, no clinically meaningful differences in the pharmacokinetics, efficacy, or safety in patients with treatment-emergent anti-ranibizumab antibodies were observed. Therefore, a similar PK profile was not observed in the clinical trials. Approval is recommended.

8. Assessment of Effectiveness

Ranibizumab, (b) (4) 0.5 mg dosed intravitreally q4 weeks have been demonstrated to be safe and effective in multiple adequate and well controlled clinical trials. A single, adequate and well controlled trial, Ladder, was conducted to explore different doses in the port delivery system. A single, adequate and well controlled trial, Archway, was conducted to confirm the efficacy and demonstrate the ability to refill the port delivery system.

8.1 Dose and Dose Responsiveness

Final Study Report GX28228, (Ladder) A Phase II, multicenter, randomized, active treatment-controlled study of the efficacy and safety of the Port Delivery System with ranibizumab for sustained delivery of ranibizumab in patients with subfoveal neovascular age-related macular degeneration.

8.2 Clinical Trials Intended to Demonstrate Efficacy

Primary CSR Study GR40548, (Archway): A Phase III, Multicenter, Randomized, Visual Assessor-Masked, Active Comparator Study of the Efficacy, Safety, and Pharmacokinetics of the Port Delivery System with Ranibizumab in Patients with Neovascular Age-Related Macular Degeneration.

Demographics

The demographics of patients enrolled the two adequate and well controlled studies are displayed below.

Table 6. Baseline Demographics and Clinical Characteristics

	Archway		**Ladder**			
Characteristic	Susvimo 100 mg/mL Q24w (N=248)	Intravitreal Ranibizumab 0.5 mg (N=167)	Ranibizumab 10 mg/mL (N=58)	Ranibizumab 40 mg/mL (N=62)	Ranibizumab 100 mg/mL (N=59)	Intravitreal Ranibizumab 0.5mg (N=41)
Sex, n (%)						
Male	103 (42%)	67 (40%)	22 (38%)	23 (37%)	21 (36%)	13 (32%)
Female	145 (58%)	100 (60%)	36 (62%)	39 (63%)	38 (64%)	28 (68%)
Age, years						
Mean (SD)	75 (8)	75 (8)	74 (8)	76 (8)	75 (8)	72 (9)
Median (min, max)	75 (51, 96)	75 (54, 89)	76 (56,92)	76 (50,90)	75 (57,91)	74 (52,85)
Age groups (years), n (%)						
≥17 to <65	26 (10%)	17 (10%)	8 (14%)	7 (11%)	9 (15%)	7 (17%)
≥65 to <75	81 (33%)	57 (34%)	15 (26%)	18 (32%)	19 (32%)	16 (39%)
≥75	141 (57%)	80 (48%)	35 (60%)	37 (57%)	31 (53%)	18 (44%)
Race, n (%)						
White	240 (97%)	161 (96%)	57 (98%)	61 (98%)	56 (95%)	41 (100%)
Asian	1 (0.4%)	0	0	0	2 (3%)	0
Black/African American	3 (1%)	1 (1%)	1 (2%)	0	0	0
Other	4 (2%)	5 (3%)		1 (2%)	1 (2%)	0
Ethnicity, n (%)						
Hispanic	7 (3%)	8 (5%)	3 (5%)	3 (5%)	2 (3%)	1 (2%)
Non-Hispanic	241 (97%)	159 (95%)	55 (95%)	56 (90%)	57 (97%)	39 (95%)
ETDRS BCVA						
Mean (SD)	74 (10)	75 (10)	69 (13)	70 (12)	70 (10)	71 (13)
Median	77	78	72.5	71.5	72	73

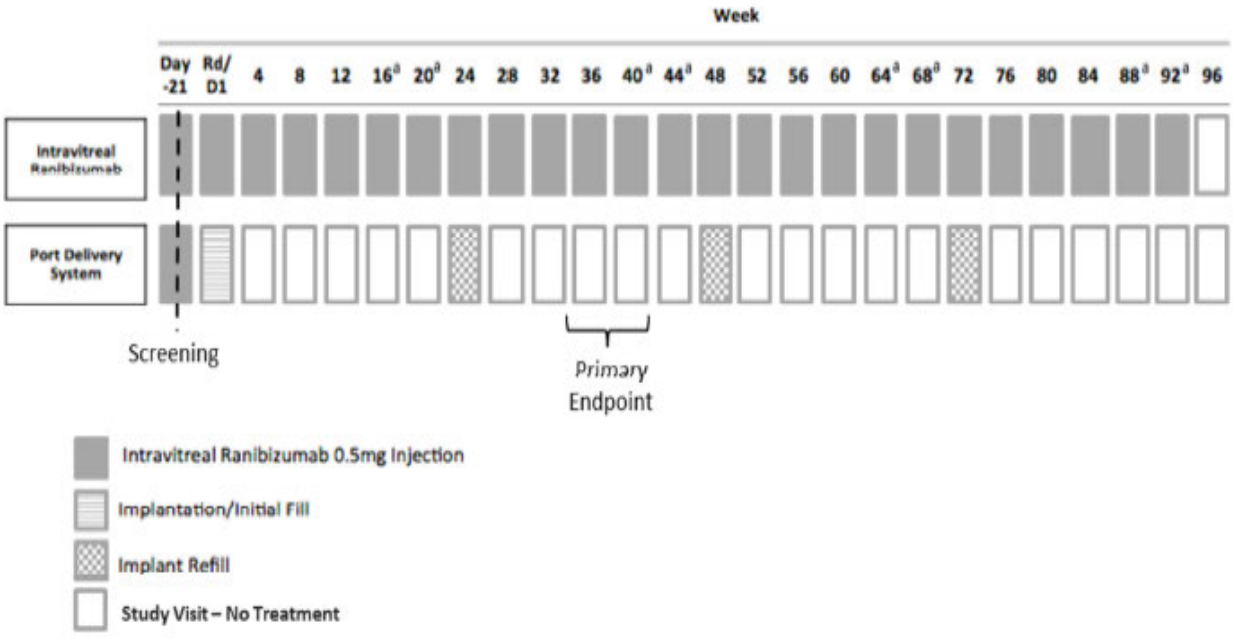
	Archway		**Ladder**			
Characteristic	Susvimo 100 mg/mL Q24w (N=248)	Intravitreal Ranibizumab 0.5 mg (N=167)	Ranibizumab 10 mg/mL (N=58)	Ranibizumab 40 mg/mL (N=62)	Ranibizumab 100 mg/mL (N=59)	Intravitreal Ranibizumab 0.5mg (N=41)
Min-Max	35-92	35-94	34-87	34-88	37-85	34-88
>=74	163 (66%)	113 (68%)				
>=66			43 (74%)	43 (69%)	41 (70%)	30 (73%)
Center Point Thickness						
Mean (SD)	177 (55)	177 (49)	194 (73)	182 (73)	183 (69)	185 (62)
Median	169.5	171.0	187.5	171	161	174
Number of anti-VEGF injections prior to first Study Treatment						
Mean (SD)	5.0 (2.1)	5.0 (1.5)	2.7 (1.2)	2.8 (1.2)	3.1 (1.5)	2.9 (1.3)
Median	4.0	4.0	2	2	3	2
Min-Max	3 - 31	4 - 9	2-7	2-6	2-8	2-7
Number of anti-VEGF injections prior to first Study Treatment						
1	0	0	0	0	0	0
2	0	0	37 (64%)	37 (60%)	27 (46%)	23 (56%)
3	1 (0.4%)[a]	0	7 (12%)	8 (13%)	17 (29%)	8 (20%)
4	137 (55.2%)	99 (59.3%)	10 (17%)	10 (16%)	4 (7%)	5 (12%)
5	49 (19.8%)	21 (12.6%)	2 (3%)	4 (7%)	4 (7%)	2 (5%)
6	26 (10.5%)	17 (10.2%)	1 (2%)	3 (5%)	6 (10%)	2 (5%)
7	21 (8.5%)	11 (6.6%)	0	0	0	0
8	7 (2.8%)	13 (7.8%)	0		1 (2%)	0
9	4 (1.6%)	6 (3.6%)				
10	1 (0.4%)					
11	1 (0.4%)					
31	1 (0.4%)					
Time Since First Diagnosis of Neovascular AMD (Months)						
Mean (SD)	5.9 (9.5)	5.3 (2.0)	3.4 (2.0))	3.2 (1.5)	3.9 (2.1)	3.4 (1.8)
Median	4.6	4.5	2.5	2.5	3.0	2.3
Min-Max	3 - 152	3 - 10	1.0-10.5	1.9-7.6	1.9-10.2	1.3-8.6

Source: Study Report Table 18

Archway Trial

Design, Archway Trial

Study GR40548 (Archway) is an ongoing Phase III, randomized, multicenter, open-label (visual acuity assessor [VAE] masked), active comparator study designed to assess the efficacy, safety, and pharmacokinetics of ranibizumab 100 mg/mL Q24W delivered via the PDS compared with ranibizumab intravitreal 0.5 mg injections every 4 weeks (Q4W) in patients with neovascular age related macular degeneration (nAMD).



D=day; Rd=randomization.

[a] Patients in the Implant arm may be eligible for rescue treatment with open-label ranibizumab (0.5 mg intravitreal injections of 10 mg/mL ranibizumab) at Weeks 16, 20, 40, 44, 64, 68, 88, and 92.

- At selected sites, an additional PK sample were to be collected from patients in the intravitreal arm 1-5 days after an intravitreal ranibizumab 0.5 mg injection in order to collect a sample near C_{max} (Protocol Section 3.5.4 and Appendix 2)
- The secondary endpoint of proportion of patients who lost < 15 letters in best corrected visual acuity (BCVA) from baseline over week 36 and week 40 and overtime was removed
- Language was added to clarify that it would be challenging to fully mask site staff in an open-label surgical study and measures taken to maintain VA examiner masking as best as possible were implemented.

Eligibility Criteria, Archway Trial

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

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

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

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

5. Patients diagnosed with nAMD in the study eye within 9 months prior to screening who had been treated with at least 4 intravitreal anti-VEGF injections within 6 months prior to screening, with the most recent dose being ranibizumab

Reviewer's Comments: *The eligibility criteria were recognized by the Agency as a potential problem part way through the clinical trial. While the inclusion/exclusion criteria required both a diagnosis of nAMD within the past 9 months and a demonstration that the subject had demonstrated a response to anti-VEGF treatment sometime in the past, there was no criterion that ensured than the subject needed continued treatment with an anti-VEGF product. It is recommended that in future trials, a minimum visual acuity threshold be set at less than 75 letters on the ETDRS chart.*

Statistical Analysis Plan, Archway Trial

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

- Population: Adult patients with nAMD diagnosed within 9 months and receiving at least 4 anti-VEGF intravitreal injections (with the last injection being ranibizumab), responsive to prior anti-VEGF treatment

- Variable: Change in BCVA score from baseline averaged over Weeks 36 and 40
- Intercurrent events: Regardless whether or not a patient had the following intercurrent event prior to Week 40:
  - Received more than 1 supplemental treatment
  - Received any prohibited systemic treatment or prohibited therapy in the Study eye (Protocol Section 4.4.2)
  - Discontinued study treatment due to AEs
  - Discontinued study treatment due to lack of efficacy as per investigator’s clinical judgment
- Population-level summary: Difference in adjusted mean between PDS and intravitreal arms

The primary objectives were to determine the non-inferiority and equivalence between the 2 treatment arms, as measured by the primary efficacy endpoint with an equivalence 95% confidence interval of ±4.5 letters. To control the overall type I error, a fixed sequence testing procedure (Westfall and Krishen 2001) was used. If the PDS 100 mg/mL arm was shown to be non-inferior

to the intravitreal arm at the one-sided 0.02485 level, then the equivalence test was to be conducted using 2 one-sided 0.02485 tests. All confidence intervals were two-sided and at the 95.03% level to adjust for the interim safety monitoring by the iDMC. The primary analysis was performed using the mixed-effect model with repeated measures (MMRM) based on all available data up to Week 40. All observed measurements were included in the analysis whether or not a patient had an intercurrent event. Missing data were implicitly imputed by the MMRM model, assuming a missing at random mechanism.

Reviewer's Comments: *Multiple sensitivity analyses were performed. None of the sensitivity analyses produced a result which called into question the primary analysis.*

Results of Analyses, Archway Trial

Table 7. Patient Screening and Randomization, Archway

Disposition	
No. patients screened	619
No. patients not randomized	201
No. screening failures	201/619 (32%)
No. patients randomized	418

Source: Study Report GR40548 Section 4.1

A total of 619 patients were screened. Of these, 201 were considered screen failures (the main reasons for screen failure were lack of response to anti-VEGF treatment during run-in phase for patients who had not received at least 3 prior anti-VEGF treatments [n=50], subfoveal fibrosis or atrophy [n=35] and lack of ability and willingness to undertake all scheduled visits and assessments [n=18]) 418 patients were enrolled and randomized (251 to the PDS 100 mg/mL arm and 167 to the intravitreal arm). Three patients randomized to the PDS 100 mg/mL arm were never treated (one patient was unable to attend the Day 1 visit in the stipulated timeframe, one experienced atrial fibrillation and was unable to comply with study visits, and one did not have nAMD diagnosis within 9 months).

The Efficacy and Safety populations therefore comprised 415 patients (248 in the PDS 100 mg/mL arm and 167 in the intravitreal arm). Prior to Week 40, 2 patients in the PDS 100 mg/mL arm and 5 in the intravitreal arm discontinued the study. The most common reason for study discontinuation in the intravitreal arm was withdrawal by patient (n=4). Three patients died on study (2 in the PDS 100 mg/mL arm and 1 in the intravitreal arm). One additional patient in the intravitreal arm withdrew from the study at Day 187 and later died of pancreatic carcinoma.

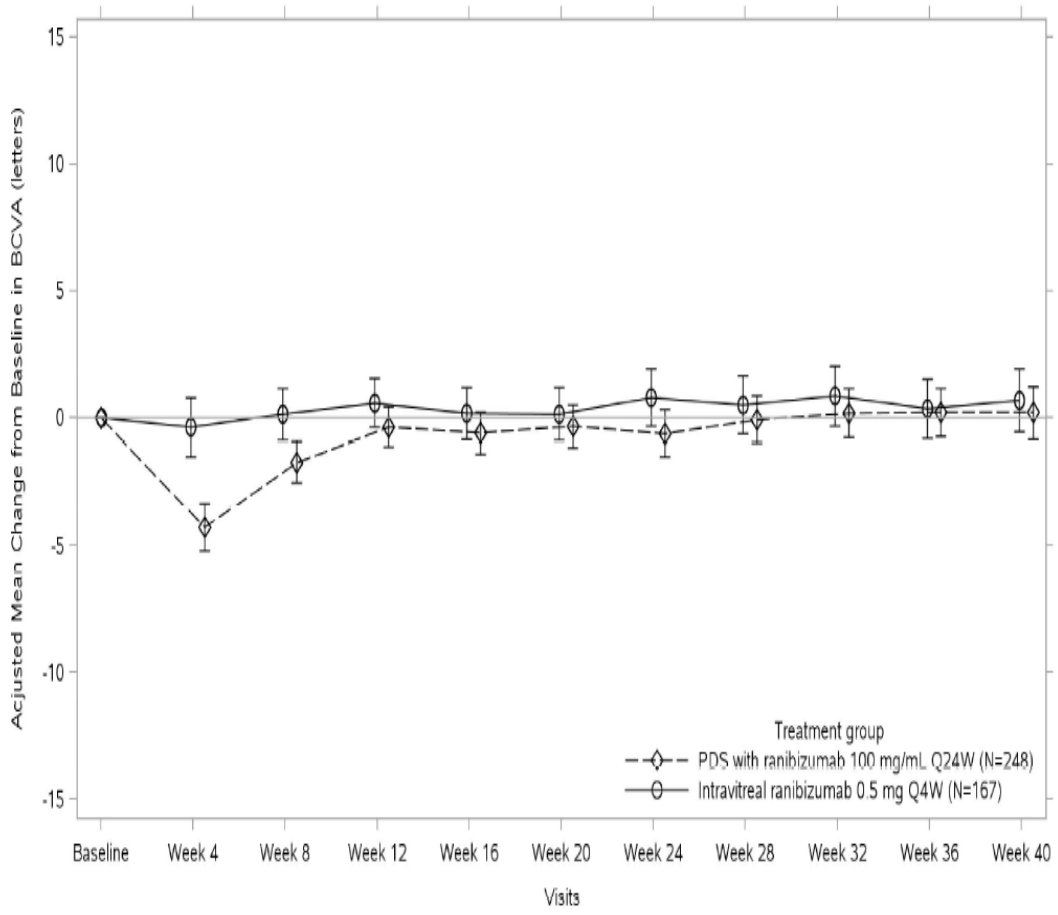
Table 8. Patient Disposition, Archway

Disposition Category	100 mg/mL Port	0.5 mg
Patients randomized	251	167
Treated	248	167
Completed Week 40	246	162
Continuing past Week 40	240	160
Adverse Event (see table below)	5	0
Death	2	1
Withdrawal by subject	0	4
Physician decision	0	1

Source: Study Report GR40548 Section 4.1

The causes of death in the 100 mg/mL Port arm were cardiac arrest and acute respiratory failure. The cause of death in the 0.5 mg arm was pancreatic carcinoma.

Adjusted Mean Change in Best Corrected Visual Acuity over Time (Observed Data): MMRM Method



MMRM=Mixed-effect model with repeated measures. The model was adjusted for treatment group, visit, treatment by visit interaction, baseline BCVA score (continuous), baseline BCVA score (<74 letters vs ≥74 letters).

Reviewer's Comments: *There is a post-operative drop in visual acuity of approximately 5 letters, which does not catch up to the q4w dosing until week 12. After week 12, the efficacy between the groups are equivalent.*

Primary Endpoint Best Corrected Distance Visual Acuity at Week 36-40

	PDS 100 mg/mL Arm Adjusted Mean (95.03% CI)	**Intravitreal Arm Adjusted Mean (95.03% CI)**	**Difference in Adjusted Means (95.03% CI)**
Primary Analysis (Efficacy Population)			
MMRM method based on Treatment Policy Estimand	0.2 (-0.7, 1.1)	0.5 (-0.6, 1.6)	-0.3 (-1.7, 1.1)
Supplemental Analyses (Efficacy Population)			
Trimmed mean method with ANCOVA	2.8	3.3	-0.5 (-1.4, 0.4)
MMRM method using different rules for measures after intercurrent events: "had > 1 supplemental treatment" and "had prohibited therapy"			
Method 1: Imputed using LOCF	0.1 (-0.9, 1.0)	0.5 (-0.6, 1.6)	-0.5 (-1.9, 1.0)
Method 2: Assessments after 2 or more supplemental treatments or prohibited treatments excluded	0.1 (-0.8, 1.0)	0.5 (-0.6, 1.6)	-0.4 (-1.8, 1.1)
Sensitivity Analysis (Per Protocol Population)			
MMRM method based on treatment policy estimand	0.2 (-0.8, 1.1)	0.6 (-0.6, 1.7)	-0.4 (-1.8, 1.1)

Intercurrent Events

	100 mg/mL Port Delivery N=248	Ranibizumab 0.5 N=167
Total number of patients with at least one type of intercurrent event*	7 (3%)	0
Received more than one supplemental treatment in Study Eyes	1 (0.4%)	0
Received prohibited therapy	4 (2%)	0
Discontinued due to Adverse Event	5 (2%)	0

* All events on or prior to Day 294 (last day of Week 40 analysis visit window).

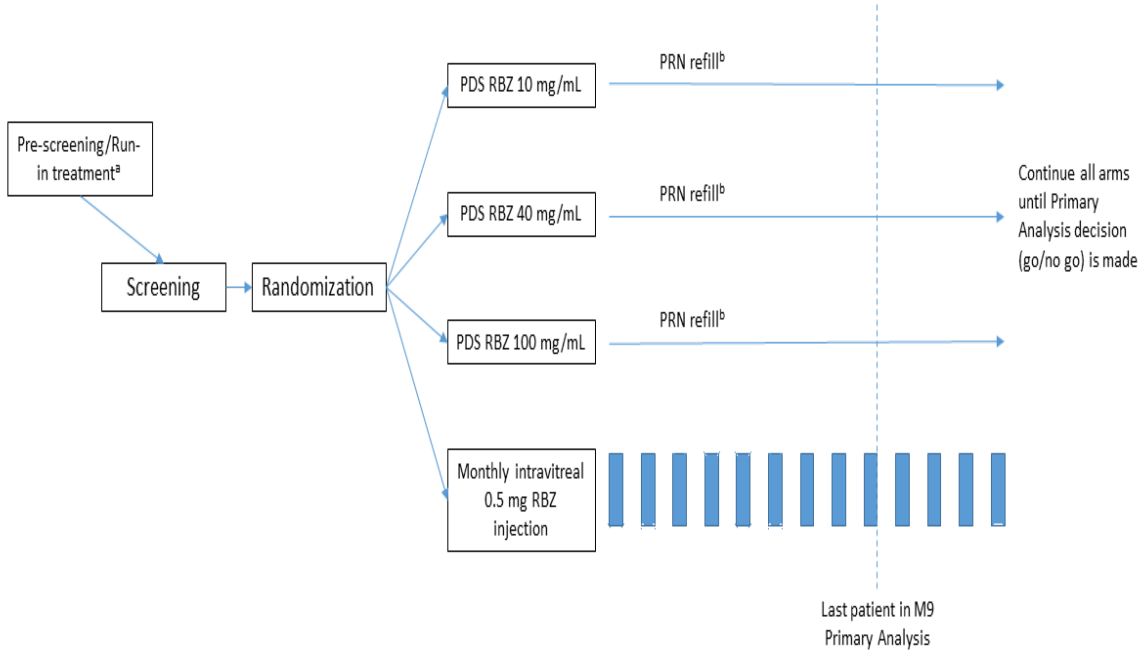
** Prohibited therapy is concurrent use of any systemic anti-VEGF agents or any protocol defined prohibited study eye therapy.

*** Lack of Efficacy is by investigator judgment for efficacy analyses. Lack of efficacy, progressive disease, disease relapse, symptomatic deterioration are combined as lack of efficacy.

Ladder Trial

Design of Ladder Trial

Study GX28228 was a Phase II, multicenter, dose-ranging, randomized, active treatment controlled study. Patients were randomized 3:3:3:2 to Port Delivery System with ranibizumab (PDS) 10 mg/mL, 40 mg/mL, or 100 mg/mL, or control (0.5 mg monthly intravitreal injections of 10 mg/mL formulation [hereinafter referred to as the intravitreal arm]). The study included pre-screening, screening, and randomization visits followed by the treatment period. The oral thrombotic substudy enrolled patients requiring oral antithrombotic therapy. All patients in the substudy received PDS 100 mg/mL



Refill Criteria

Starting at the Month 1 visit, all randomized patients were assessed monthly for refill. At 1 month after initial fill, patients randomized to the PDS arms had their implant refilled only if **any** of the following criteria was met:

- Decrease of ≥10 letters in BCVA at the current visit compared with the baseline BCVA, due to nAMD disease activity OR
- Increase in CFT of ≥100 µm at the current visit compared with the baseline CFT, due to nAMD disease activity OR
- Presence of new macular hemorrhage, due to nAMD disease activity

For subsequent assessments, patients randomized to the PDS arms had their implant refilled only if **any** of the following criteria was met:

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

- Increase in CFT of ≥100 µm from the lowest CFT measurement on study, due to nAMD disease activity OR
- Decrease of ≥5 letters in BCVA at the current visit compared with the average BCVA over the last 2 available measurements, due to nAMD disease activity OR
- Decrease of ≥10 letters from best recorded BCVA on study, due to nAMD disease activity OR
- Presence of new macular hemorrhage, due to nAMD disease activity CFT measurements used to determine need for refill were assessed by the investigator.

The following are protocol amendments which occurred after patients had been enrolled.

Protocol Version	**Summary of Major Changes**
Version 4 (8 December 2015)	• Amendment to the inclusion/exclusion criteria and the schedule of assessments
Version 5 (18 February 2016)	• Amendment to include a gated approach to patients' enrollment, to enable real-time review of post-implant insertion safety data by the Internal Monitoring Committee.
Version 6 (30 August 2016)	• Amendment to update the refill criteria and lack of clinical efficacy criteria and to include language for a potential, flexible interim analysis.
Version 7 (4 May 2017)	• The AMD diagnosis window increased from 6 to 9 months before the screening visit to allow patients who received a longer duration of treatment with intravitreal injections to be enrolled in the study. • The mandatory explantation of implants for patients who meet lack of clinical efficacy criteria was removed following internal assessment of explanted implants that suggested that lack of clinical efficacy was unlikely to be associated with inadequate device performance or failure. • Non-inferiority testing for change from baseline in BCVA at Month 9 between the intravitreal and the PDS arms was removed. This change did not influence the primary or secondary endpoints, sample size, power, or the statistical methods, with the exception of removing
Version 8 (7 February 2018)	• Study duration for patients in the intravitreal arm extended by approximately 4 months to align with the other treatment arms and to allow for continued monthly evaluation and study treatment.

Given the exploratory nature of this study, the Protocol allowed for the possibility of up to 2 interim analyses. The first interim was performed after ~50% of patients completed the 6-month follow-up in October 2017 and the second interim was performed after ~70% of patients completed the 9-month follow-up in April 2018 in order to determine the PDS clinical development plan. The decisions to conduct optional interim analyses and the timing of the analyses were documented in the IMC Agreement prior to the conduct of the interim analyses.

Eligibility Criteria, Ladder

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

1. Newly diagnosed nAMD patients who are treatment naïve. These patients will undergo pre-screening if they satisfy eligibility criteria and sign informed consent. During the pre-screening, patients will receive two ranibizumab ITV treatments to determine if they demonstrate response (Decrease in CFT of >50 µm since commencing ITV anti-VEGF treatment OR Stable or improved BCVA since commencing ITV anti-VEGF treatment) to ranibizumab treatment as outlined per the eligibility criteria.

2. Patients diagnosed with nAMD in the study eye within 9 months prior to screening who have been treated with a single anti-VEGF ITV injection. These patients may receive one "run-in" ITV ranibizumab treatment prior to screening if they satisfy eligibility criteria and sign the informed consent form.

3. Patients diagnosed with nAMD in the study eye within 9 months prior to screening who have been treated with no more than eight anti-VEGF ITV injections and with the most recent dose being aflibercept or bevacizumab. These patients may receive one "run-in" ITV ranibizumab treatment prior to screening if they satisfy eligibility criteria and sign the informed consent form.

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

Dosing Guidelines Prior to Screening

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

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

Statistical Analysis Plan, Ladder

The primary endpoint was time from implant insertion until a patient first required implant refill according to protocol-defined refill criteria (TTFR). For patients who did not meet the protocol-defined refill criteria on or before the analysis cut-off date, the time of refill was censored. The censoring date was defined as the date of a patient's last visit on or before the cut-off date, or the date when the patient discontinued from the study, whichever occurred first. Observed data were used for these analyses.

Time to first refill was also censored for the following patients:

- At the time of an intravitreal anti-VEGF injection in the study eye if administered before the first refill
- At the time the refill criteria could not be assessed, which was defined as at least 2 refill variables (BCVA, CFT, or new macular hemorrhage) unable to be evaluated for any reason, or were affected by a clinical reason different from nAMD activity, before the first refill
- At the time of explant

To support the dose level selection among the implant groups for future trials, the difference in time to first required refill between each of the following pairs of PDS arms were assessed using a log-rank test stratified by baseline BCVA score (≤ 65 letters vs. ≥66 letters) and number of prior anti-VEGF intravitreal injections (≤3 vs. ≥4), at a one sided significance level of 15%:

- PDS 100 mg/mL versus PDS 10 mg/mL
- PDS 100 mg/mL versus PDS 40 mg/mL
- PDS 40 mg/mL versus PDS 10 mg/mL

In addition, the Hazard Ratio (HR) and its corresponding 70% CI for each pairwise comparison of the PDS arms was estimated using a Cox proportional hazards model stratified by baseline BCVA score (≤65 letters vs. ≥66 letters) and number of prior anti-VEGF intravitreal injections (≤3 vs. ≥4) with main effects for treatment. Kaplan-Meier estimates for time to first required refill were presented graphically by the PDS arm. Median time to first meeting refill criteria was calculated for each PDS arm with the corresponding 80% CI.

Results of Analyses, Ladder

Table 9. Patient Screening and Randomization, Ladder Trial

Disposition	
Number patients screened	374
Number patients not randomized	30
Number enrolled	244
Excluded from site #290667	7
Oral antithrombotic substudy	12 enrolled/11 treated
Number patients randomized	225

Source: [t_anlpop, t_ds_m10, t_ds]

Table 10. Patient Disposition, Ladder

Disposition Category	Ranibizumab 10 mg/mL (N=58)	Ranibizumab 40 mg/mL (N=62)	Ranibizumab 100 mg/mL (N=59)	Ranibizumab 0.5mg Monthly (N=41)
Patients randomized	63	63	63	43
Randomized	59	62	63	41
Efficacy population	58	62	59	41
Safety population	58	62	59	41
Discontinued study drug	10 (17%)	7 (11%)	3 (5%)	5 (12%)
Adverse event	2 (3%)	3 (5%)	1 (2%)	0
Lack of efficacy	5 (9%)	2 (3%)	1 (2%)	0
Discontinued study	10 (17%)	7 (11%)	3 (5%)	5 (12%)
Adverse event	2 (3%)	3 (5%)	1 (2%)	
Death	0	1 (1.6%)	1 (1.7%)	1 (2%)
Lack of Efficacy	5 (9%)	2 (3%)	1 (1.7%)	
Subject withdrawal		1 (1.6%)		3 (7%)
Physician decision	1 (1.7%)			
Other	2 (3%)			1 (2%)

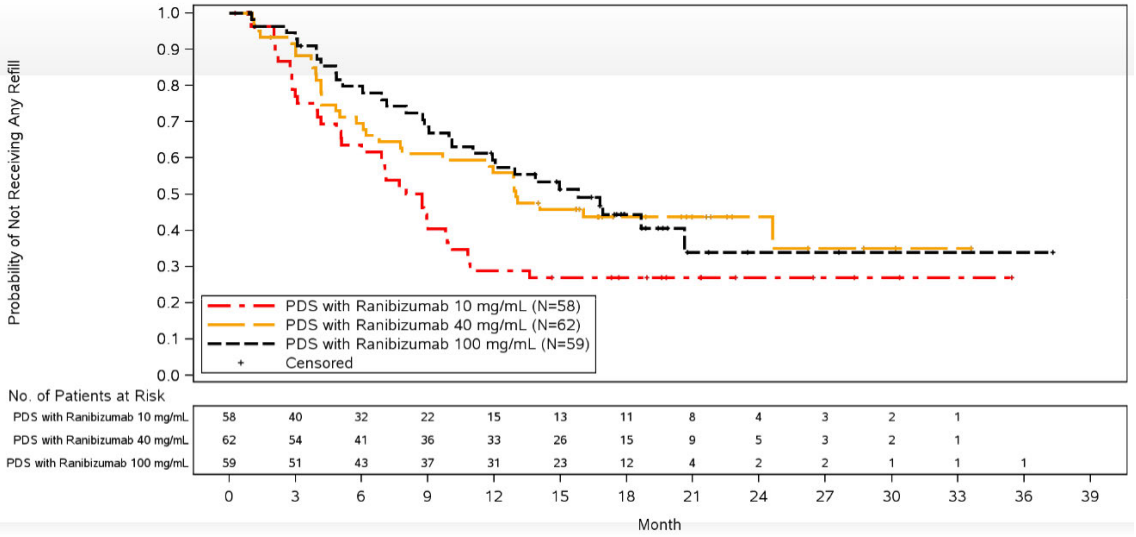
Source: [Clinical data scientist to provide all standard tables and figures]
Abbreviation: mITT, modified intention-to-treat; N, number of subjects; n, number of subjects with at least one event

Time to First Required Refill (TTFR) (Efficacy Population)

	10 mg/mL	40 mg/mL	100 mg/mL
Median, months	8.7	13.0	15.8
Hazard Ratio (70% Confidence Interval), Log-rank p-value			
vs. PDS 10 mg/mL		0.67 (0.52, 0.85) p=0.0875	0.56 (0.43, 0.72) p=0.0166
vs. PDS 40 mg/mL			0.89 (0.69, 1.15) p=0.6374

The p-values were from stratified log-rank tests. The HR for each pairwise comparison of the treatment arms was estimated using the Cox proportional hazards model. Both analyses are stratified by baseline best corrected visual acuity (BCVA) score (≤65 letters vs. ≥66 letters) and number of prior anti-VEGF intravitreal injections (≤3 vs. ≥4).
Sources: Campochiaro et al. 2019 (primary analysis datacut), t_ef_tte (final analysis)

Kaplan-Meier Plot of Time to First Required Refill at Final Analysis (Efficacy Population)



Event Free Rate

Month	10 mg/mL	40 mg/mL	100 mg/mL
3	77%	92%	93%
4	73%	82%	88%
5	67%	71%	82%
6	61%	70%	80%
7	58%	65%	76%
8	52%	61%	74%
9	42%	61%	69%
10	37%	59%	65%
11	29%	59%	63%
12	29%	56%	59%

(1) Stratified log-rank test at a one-sided significance level of 15%. The HR for each pairwise comparison of the treatment arms is estimated using a Cox proportional hazards regression model. Both analyses are stratified by baseline BCVA score (<=65 letters vs. >=66 letters) and number of prior anti-VEGF ITV injections (<=3 vs. >=4). Estimated HRs for each pairwise comparison are presented with corresponding 70% CIs.
(**)Subjects who have experienced first refill events or withdrew from the study are not counted as "at risk".
(2) Comparison of Implant with 40 mg/mL versus Implant with 100 mg/mL. The censoring date is defined as the date of a patient's last visit before the cutoff date or the date when the patient discontinues from the study, whichever occurs first. Time to first meeting protocol-defined criteria is also censored for patients meeting the following situations:
-At the time of an ITV anti-VEGF injection in study eye if administered before the first required refill.
-At the time the refill criteria cannot be assessed, which is defined as at least two refill variables (BCVA, CFT, or new macular hemorrhage) cannot be evaluated for any reason, or are affected by a clinical reason different from nAMD activity, before the first required refill.

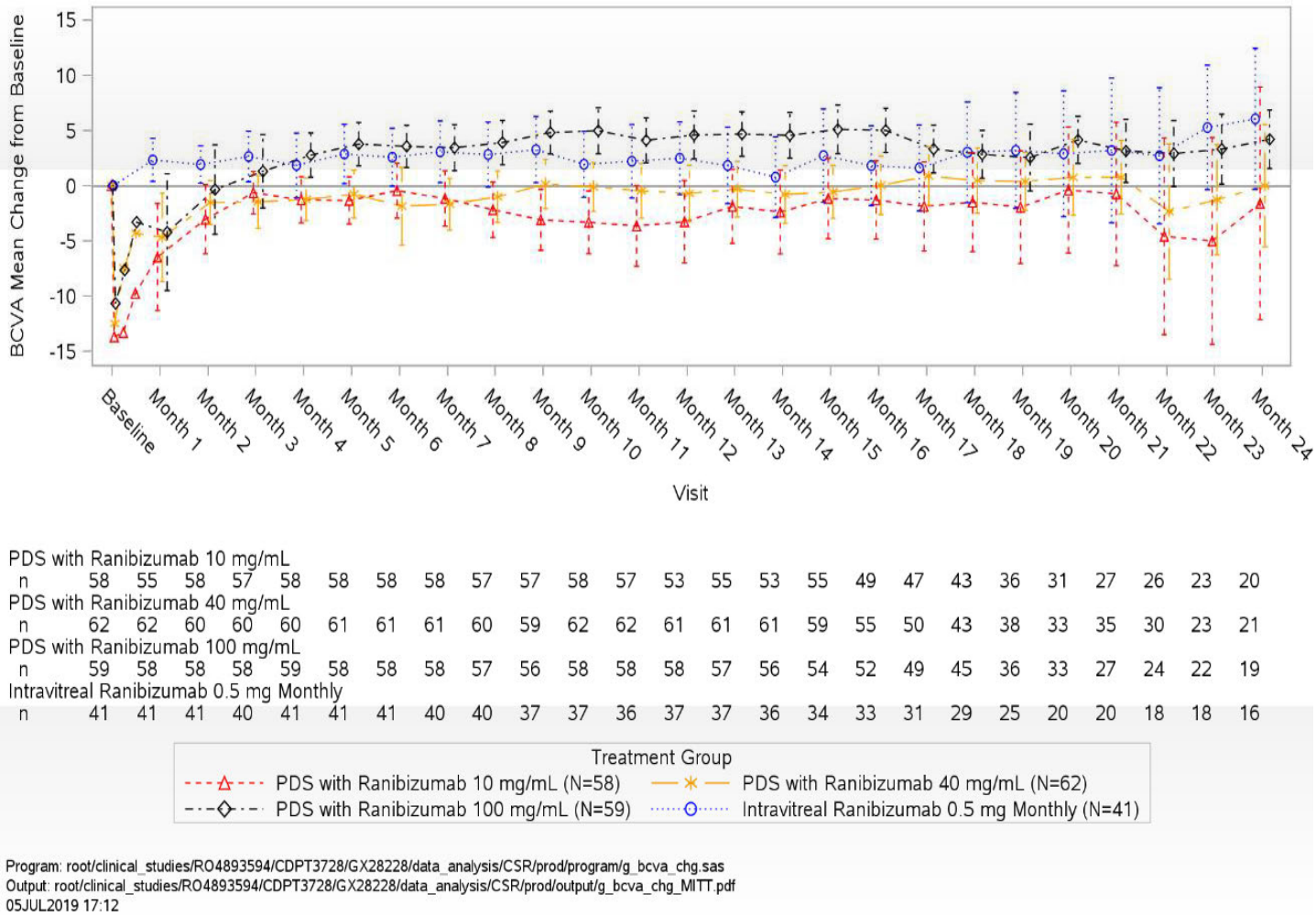
Overall, 43 dosing errors were reported in 33 patients (15 in 15 patients in the PDS 10 mg/mL arm, 14 in 10 patients in the PDS 40 mg/mL arm and 14 in 8 patients in the PDS 100 mg/mL arm) (l_pt_doseerr_SE). The most frequently reported dosing error was due to CFT measurement error in 26 patients (13 in 13 patients in the PDS 10 mg/mL arm, 12 in 8 patients in the PDS 40 mg/mL arm

and 7 in 5 patients in the PDS 100 mg/mL arm). Dosing errors were also reported due to incorrect assessment of nAMD activity (2 refills in 2 patients in the 40 mg/mL arm) and incorrect assessment of new macular hemorrhage (5 refills in 1 patient in the 100 mg/mL arm).

	10 g/mL (N=58)	40mg/mL (N=62)	100 mg/mL (N=59)
Number of patients meeting ≥1 refill	39 (67.2%)	25 (40.3%)	22 (37.3%)
Number of visits refill criteria met	78	53	43
BCVA only[a]	15 (19.2%)	14 (26.4%)	11 (25.6%)
CFT only[a]	39 (50.0%)	24 (45.3%)	19 (44.2%)
New macular hemorrhage only[a]	1 (1.3%)	1 (1.9%)	7 (16.3%)
BCVA and CFT[a]	20 (25.6%)	10 (18.9%)	3 (7.0%)
BCVA and new macular hemorrhage[a]	0	0	0
CFT and new macular hemorrhage[a]	1 (1.3%)	4 (7.5%)	0
BCVA, CFT, and new macular	2 (2.6%)	0	3 (7.0%)

BCVA=best corrected visual acuity; CFT=central foveal thickness;

[a] Percentage is with respect to the total number of times the refill criteria were met. Source: t_ex_rf_m10_SE



Descriptive Summary of Change from Baseline in BCVA at Month 9 with and without Censoring at the Final Analysis (Efficacy Population)

	10 mg/mL	**40-mg/mL**	**100 mg/mL**	**Ranibizumab 0.5 mg**
Change from baseline in BCVA at Month 9, observed data without censoring				
Mean	-3.1	+0.2	+4.8	+3.3
Difference in Means (vs. ITV 0.5 mg Monthly) (95% CI)	-6.4 (-10.5, -2.2)	-3.1 (-6.7, 0.5)	+1.6 (-1.8, 4.9)	

BCVA=best corrected visual acuity; CI=confidence interval; Source: t_va_mmrm_obs_nc, t_va_mmrm

Censoring had no significant effect on the results.

8.3 Statistical Review

(from Elena Rantou's Biometrics Review)

The efficacy of Susvimo was evaluated in the pivotal, Phase 3 randomized, multicenter, open-label, active comparator clinical trial, GR40548, the Phase 3 long-term, extension, multicenter, open-label, visual-assessor (VA) masked, multiple-cohort, extension study GR40549, and the Phase-2, dose-ranging, randomized, active treatment-controlled, multicenter, ladder main study GX20228. The safety of Susvimo was the primary objective of the sub-study of GX28228, a Phase-2, non-randomized, uncontrolled, open-label, sub-study.

For study GR40548 (Archway), a total of 418 eligible patients were randomized in a 3:2 ratio and 415 of them received treatment. On the day of randomization visit best-corrected visual acuity (BCVA) score is measured and randomization is stratified by BCVA score (<74 letters vs. ≥74 letters). For each patient one eye is chosen for the study treatment.

The primary efficacy endpoint is the change in BCVA score from baseline averaged over Weeks 36 and 40. PDS 100 mg/mL is considered non-inferior to intravitreal treatment if the lower limit of the 95% confidence interval for the treatment difference in the change in BCVA score from baseline averaged over Weeks 36 and 40 is > -4.5 letters. Another primary objective is to show equivalence of the two treatments. This is accomplished when the 95% confidence interval (CI) for the difference in mean change BCVA from baseline averaged over the Weeks 36 and 40 is contained within ±4.5 letters. To control for the overall Type-I error rate, a fixed-sequence testing procedure was used adjusting the one-sided significance level to 0.02485, which leads to a 95.03% confidence coefficient.

In study GR40548 (Archway), the PDS 100 mg/mL group was statistically non-inferior to the ranibizumad intravitreal (RBZ ITV SOC 0.5MG) group with respect to the change from baseline in BCVA averaged over Weeks 36 and 40. The change from baseline in BCVA averaged over Weeks 36 and 40 was lower in the PDS arm compared to the intravitreal arm by 0.33 (95% CI: -1.58 to 0.92). The lower limit of the 95% CI is greater than -4.5 and both limits of the CI are contained within [-4.5, 4.5] indicating that both the non-inferiority and the equivalence criteria for the primary efficacy endpoint have been satisfied.

Similarly, in study GX28228 (Ladder), the PDS 100 mg/mL group was statistically non-inferior to the RBZ ITV SOC 0.5MG (intravitreal) group with respect to the change from baseline in BCVA averaged over Months 9 and 10. As shown in Table 1 the change from baseline in BCVA averaged over Months 9 and 10 was higher in the PDS arm compared to the intravitreal arm by 1.84 (95% CI: -(-1.48, 5.16)). The lower limit of the 95% CI is greater than -4.5 indicating non-inferiority of the PDS to the intravitreal arm.

Table 11: Summary of the change from baseline in BCVA averaged over Weeks 36 and 40 (Efficacy population [b])

	GR40548			GX28228	
PDS 100 mg/mL (N=248)	ITV SOC 0.5MG (N=165)	Difference[a] (95% CI)	PDS 100 mg/mL (N=59)	ITV SOC 0.5MG (N=41)	Difference (95% CI)
0.19 (0.40)	0.52 (0.49)	-0.33 (-1.58,0.92)	4.92 (1.07)	3.08 (1.30)	1.84 (-1.48, 5.16)

[a] Least squares means (SE), differences and CI were based on a MMRM model with baseline as a covariate.
[b] Efficacy population included all randomized patients who received the study treatment.
Source: Reviewer's analysis

The PDS 100 mg/mL treatment arm showed comparable results to the ITV 0.5 MG arm regarding the change from baseline in BCVA based on the results from Study GR40548. Study GX28228 also provided supporting evidence for the same comparison. Based on the pivotal study results, the largest difference between the mean CFB in BCVA between the two arms was observed at Week 4, whereas the smallest difference was observed at Week 36. The summary of the CFB in BCVA at pre-specified timepoints based on 4 week intervals, for both Studies GR40548 and GX28228 is shown in Table 2 below.

Table 12: Summary of the CFB in BCVA over time in Studies GR40548 and GX28228 (Efficacy population [a])

GR40548	**ITV SOC 0.5MG** **N** **Mean (SD)** **Median** **(Min, Max)**	**PDS 100 mg/mL** **N** **Mean (SD)** **Median** **(Min, Max)**	**GX28228**	**ITV SOC 0.5MG** **N** **Mean (SD)** **Median** **(Min, Max)**	**PDS 100 mg/mL** **N** **Mean (SD)** **Median** **(Min, Max)**
Week 4	165 -0.46 (6.05) 0 (-38, 18)	246 -5.35 (10.90) -3 (-85, 18)	**Month 1**	41 2.34 (6.17) 1 (-9, 22)	58 -4.21 (20.1) 0 (-84, 17)
Week 8	165 0.03 (5.27) 0 (-18,18)	248 -2.03 (7.78) -1 (-58, 17)	**Month 2**	41 1.93 (5.37) 0 (-6, 15)	58 -0.35 (15.4) 2 (-83, 16)
Week 12	165 0.43 (5.80) 0 (-28,22)	248 -0.84 (7.45) 0 (-32, 23)	**Month 3**	40 2.65 (7.16) 2 (-19, 19)	58 1.31 (12.7) 2.5 -83 16
Week 16	165 0.15 (6.57) 0 (-29, 19)	248 -0.53 (6.45) 0 (-46, 22)	**Month 4**	41 1.85 (9.23) 0 (-37, 21)	59 2.78 (7.70) 3 (-12, 34)
Week 20	165 0.12 (6.35) 0 (-32, 17)	248 -0.59 (7.51) -1 (-34, 25)	**Month 5**	41 2.88 (8.51) 3 (-30, 19)	58 3.78 (7.46) 4.5 (-13, 36)
Week 24	165 0.68(6.79) 1 (-32, 19)	248 -2.90 (14.98) 0 (-79, 22)	**Month 6**	41 2.59 (8.28) 4 (-27, 19)	58 3.57 (7.26) 3 (-13, 32)

GR40548	ITV SOC 0.5MG N Mean (SD) Median (Min, Max)	PDS 100 mg/mL N Mean (SD) Median (Min, Max)	GX28228	ITV SOC 0.5MG N Mean (SD) Median (Min, Max)	PDS 100 mg/mL N Mean (SD) Median (Min, Max)
Week 28	165 0.51 (6.80) 0 (-36, 19)	248 -1.24 (11.46) 0 (-74, 23)	**Month 7**	40 3.08 (8.74) 2.5 (-28, 19)	58 3.45 (7.93) 4 (-19, 34)
Week 32	165 0.79 (7.32) 1 (-34, 27)	248 -0.08 (9.35) 0 (-74, 22)	**Month 8**	40 2.82 (9.21) 2 (-29, 23)	57 3.91 (7.56) 3 (-18, 33)
Week 36	165 0.25 (6.71) 0 (-35, 19)	248 0.15 (8.13) 0 (-74, 22)	**Month 9**	37 3.27 (8.99) 3 (-30, 22)	56 4.82 (7.23) 5 (-13, 35)
Week 40	165 0.58(7.04) 0 (-35, 20)	248 -0.35 (10.34) 0 (-74, 22)	**Month 10**	37 1.95 (8.95) 2 (-31, 19)	58 4.98 (7.90) 4.5 (-14, 37)

[a] Efficacy population included all randomized patients who received the study treatment.
Source: Reviewer's analysis

In summary, based on the totality of evidence from Study GR40548 and supporting evidence from Study GX28228, the reviewer concludes that the application provided substantial evidence to support the efficacy of RBZ PD 100MG/ML in patients with age-related macular degeneration (nAMD).

9. Key Review Issue Relevant to Evaluation of Benefit

Issue
Efficacy is required to be demonstrated in adequate and well controlled studies.

Background
Efficacy of ranibizumab (b) (4) 0.5mg and 2 mg, intravitreally administered monthly has already been demonstrated in adequate and well controlled studies.

Assessment
The Archway clinical trial demonstrated the non-inferiority of 100mg/mL in the port delivery system compared to monthly intravitreal injections of 0.5 mg. Mean visual acuity decreased by approximately 5 letters postoperatively, but by week 12, visual acuity measurements were the same between groups. The Ladder clinical trial, while it was underpowered to demonstrate non-inferiority of 100mg/mL compared to 0.5 mg monthly intravitreal injections, demonstrated the superiority of 100mg/mL compared to 10mg/mL.

Conclusion
Efficacy in the treatment of neovascular age related macular degeneration was demonstrated in two clinical trials.

10. Risk and Risk Management

Potential Risks or Safety Concerns Based on Drug Class

Potential or known safety risks with this product and/or the class of anti-VEFG products include the potential to develop endophthalmitis and retinal detachments following intravitreal injections. The potential to increase arterial thromboembolic events and increases in intraocular pressure.

Adequacy of Clinical Safety Database

The safety database was considered adequate for evaluation of the drug product. The safety database consisted primarily of two adequate and well controlled clinical trials, Archway and Ladder in addition to history of use of ranibizumab. The applicant has referenced the clinical trials supporting the approval of ranibizumab dosed on a monthly basis as well as the 15 year history of clinical use following approval.

Safety Findings Based on Review of Clinical Safety Database

Safety Findings and Concerns

Deaths, Archway and Ladder Trials

Table 13. Deaths in Safety Population

	Arch100	Ladder100	Ladder 40	Ladder 10	Arch 0.5	Ladder 0.5
Deaths	**N=246**	**N=59**	**N=62**	**N=58**	**N=136**	**N=41**
Total deaths	5 (%)	1	2	1	3	
Coronary artery disease	1 (%)					
Road traffic accident	1 (%)					
Unexplained	1 (%)					
Cardiac arrest	1 (%)				1	
Acute respiratory failure	1 (%)					
Non-small cell lung cancer					1	
Pancreatic carcinoma		1			1	
Chronic Obstructive Pulmonary Disease				1		
Gastric Adenocarcinoma			1			
Sepsis			1			
Congestive Cardiac Failure						1

Details

Center/Patient ID	Age/Sex/ Race	Study Group	Study Day of Death	Number of Prior Doses of Study Drug*	Days since Last Study Drug Treatment*	Reported Adverse Event that Led to Death
(b) (6)	78/M/White	Port Delivery 100	451	4	121	Coronary artery disease
	81/M/White	Port Delivery 100	366	5	12	Died in sleep
	73/F/White	Port Delivery 100	175	1	158	Cardiac arrest
	80/F/White	Port Delivery 100	523	5	0	Road traffic accident
	70/F/White	Port Delivery 100	289	2	123	Acute respiratory failure
	88/F/White	Ranibizumab 0.5	205	10	24	Pancreatic carcinoma
	71/F/White	Ranibizumab 0.5	470	16	43	Cardiac arrest
	67/M/White	Ranibizumab 0.5	489	14	127	Non-small cell lung cancer
	77/M/White	Port Delivery 10	460	4	42	Chronic obstructive pulmonary disease
	79/F/White	Port Delivery 40	515	1	515	Gastric Adenocarcinoma
	61/M/White	Port Delivery 40	520	1	520	Atrial fibrillation/Sepsis
	64/M/White	Port Delivery 100	774	3	54	Pancreatic carcinoma
	84/F/White	Ranibizumab 0.5	259	9	21	Congestive cardiac failure

Serious Adverse Events

	Arch100	Ladder100	Ladder 40	Ladder 10	Arch 0.5	Ladder 0.5
	N=248	N=59	N=62	N=58	N=167	N=41
Endophthalmitis	4	1	1	1	1	0
Vitreous Hemorrhage	2	2	2	3	1	0
Conjunctival erosion	2	1	1	1	0	0
Rhegmatogenous retinal detachment	2	1	1	1	0	0
Visual acuity reduced	3	1	1	1	0	0
Hypotony		0	1	0		0
Retinal hemorrhage		0	0	1		0
Retinal tear	1	0	0	0	1	0
Proliferative retinopathy		0	1	1		0
Tractional retinal detachment		0	0	1		0
Blurred vision		0	0	1		0
Conjunctival retraction	2	1	1	0	0	0
Conjunctival filtering bleb	1	0	1		0	0
Hyphema		0	0	1		0
Wound secretion		0	1	0		0
Intraocular pressure increased		0	0	1		
Cataract	1				0	
Retinal pigment epithelial tear	1				0	
Choroidal detachment	1				0	
Necrotising retinitis	1				0	
Corneal disorder	1				0	
Device dislocation	3				0	

Dropouts and/or Discontinuations Due to Adverse Events

Center/Patient ID-Age/Sex/Race		Adverse Event MedDRA Preferred Term		Study Day of Onset	Outcome (a)
(b) (6)	73/M/White	Conjunctival retraction	Port Delivery 100	120	Resolved
	81/M/White	Detachment of RPE	Port Delivery 100	8	Not recovered
	78/M/White	Device dislocation	Port Delivery 100	168	Resolved
	69/F/White	Device dislocation	Port Delivery 100	425	Resolved
	60/F/White	Device dislocation	Port Delivery 100	510	Resolved
	84/F/White	Drug hypersensitivity	Port Delivery 100	482	Resolved
	82/M/White	Endophthalmitis	Port Delivery 100	59	Resolved
	68/M/White	Endophthalmitis	Port Delivery 100	161	Recovered with sequelae
	71/F/White	Drug hypersensitivity	Ranibizumab 0.5	316	Not recovered
	81/M/White	Retinal hemorrhage	Ranibizumab 0.5	448	Not recovered

RPE=Retinal Pigment Epithelium

Vitreous Hemorrhages

Ladder

During the conduct of the study, an optimized version of the IFU for the surgical procedure was implemented in response to high rates of vitreous hemorrhage. The rate of vitreous hemorrhage (non-serious or serious) occurring during the postoperative period decreased from 11/22 patients (50.0%) prior to optimization to 6/157 (3.8%) after optimization.

Archway

Center/Patient ID-Age/Gender/Race		Group	Study Day of Onset	Days since Last Study Drug Treatment	Number of drug treatments	Duration
(b) (6)	- 80/M/White	Port Delivery 100	1	0	1	146
	- 91/M/White	Port Delivery 100	2	1	1	13
	- 64/M/White	Port Delivery 100	8	7	1	21
	- 65/F/White	Port Delivery 100	2	1	1	142
	- 70/F/White	Port Delivery 100	9			156
	- 76/M/White	Port Delivery 100	2	1	1	28
	- 78/M/White	Port Delivery 100	192	191	1	2
	- 68/M/White	Port Delivery 100	10	9	1	50
	- 82/F/White	Port Delivery 100	6	5	1	58
	- 75/F/White	Port Delivery 100	30	29	1	30
	- 69/F/White	Port Delivery 100	436	97	3	30
	- 89/M/White	Port Delivery 100	6	5	1	25
	- 77/F/White	Port Delivery 100	514	10	4	18
	- 70/F/White	Port Delivery 100	36	35	1	29
			333	17	8	85
	- 58/F/White	Port Delivery 100	1	0	1	72
	- 89/F/White	Port Delivery 100	3	2	1	8
		Port Delivery 100	213			48
		Port Delivery 100	400			29
		Port Delivery 100	457			27
	- 82/F/White	Ranibizumab 0.5	34	0	2	29
	- 86/F/White	Ranibizumab 0.5	197	0	8	225
	- 66/M/White	Ranibizumab 0.5	154			44
		Ranibizumab 0.5	239	14	9	22
	- 63/F/White	Ranibizumab 0.5	530	18	18	
	- 78/M/White	Ranibizumab 0.5	117	0	5	25
	- 68/F/White	Ranibizumab 0.5	534	25	19	32

Treatment-Emergent Adverse Events

Summary Adverse Events in Archway as of 11 Sept 2020

	100 mg/mL ranibizumab Port q24W	0.5 mg ranibizumab Intravitreal q4w
	N=248	N=167
Patients with ≥1 Adverse Events (AE)	246 (99.2%)	136 (81.4%)
Overall total number of AEs	1864	772
Ocular Events: Study Eye Patients with ≥1 AE	239 (96.4%)	82 (49.1%)
Total number of AEs	910	207
Patients with ≥1 Serious Adverse Event (SAE)	19 (7.7%)	4 (2.4%)
Patients with ≥1 Ocular AE leading to withdrawal from treatment	8 (3.2%)	1 (0.6%)
Ocular Events: Fellow Eye Patients with >=1 AE	104 (41.9%)	60 (35.9%)
Total number of Fellow Eye AEs	171	105
Patients with ≥1 Fellow eye SAE	3 (1.2%)	0
Non-Ocular Events: Patients with ≥1 AE	200 (80.6%)	113 (67.7%)
Total number of Non-ocular AEs		460
Patients with ≥1 Non-ocular SAE	54 (21.8%)	27 (16.2%)
Total number of deaths	5 (2.0%)	3 (1.8%)

Ocular Adverse Events: Archway and Ladder Trials

	Arch100	Ladder100	Ladder 40	Ladder 10	Arch 0.5	Ladder 0.5
	N=248	N=59	N=62	N=58	N=167	N=41
Total number of adverse events	1864	250	270	292	772	68
Total number of patients with at least one adverse event	246 (99%)	52 (88%)	58 (94%)	56 (97%)	136 (81%)	26 (63%)
Conjunctival hemorrhage	178 (72%)	36 (61%)	44 (71%)	40 (69%)	19 (11%)	8 (20%)
Conjunctival hyperemia	67 (27%)	14 (24%)	13 (21%)	17 (29%)	4 (2%)	0
Iritis	52 (21%)	7 (12%)	13 (21%)	8 (14%)	1 (0.6%)	0
Eye pain	27 (11%)	15 (25%)	12 (19%)	12 (21%)	12 (7%)	5 (12%)
Vitreous floaters	24 (10%)	11 (19%)	7 (11%)	12 (21%)	7 (4%)	4 (10%)
Foreign body sensation in eyes	19 (8%)	7 (12%)	7 (11%)	4 (7%)	2 (1%)	0
Conjunctival bleb	17 (7%)	1 (2%)	3 (5%)	3 (5%)	0	0
Vitreous detachment	16 (6%)	3 (5%)	4 (6%)	2 (3%)	12 (7%)	4 (10%)
Punctate keratitis	16 (6%)	2 (3%)	2 (3%)	4 (7%)	4 (2%)	0
Hypotony of eye	16 (6%)	1 (2%)	1 (2%)	1 (2%)	0	0
Vitreous hemorrhage	15 (6%)	6 (10%)	6 (10%)	7 (12%)	6 (4%)	0
Conjunctival oedema	13 (5%)	1 (2%)	6 (10%)	6 (10%)	0	0
Cataract	12 (5%)	10 (17%)	5 (8%)	2 (3%)	4 (2%)	5 (12%)
Blepharitis	12 (5%)	3 (5%)	1 (2%)	1 (2%)	2 (1%)	0
Anterior chamber flare	12 (5%)	3 (5%)	0	1 (2%)	1 (0.6%)	0
Corneal disorder	12 (5%)	1 (2%)	0	0	0	0
Posterior capsule opacification	11 (4%)	5 (8%)	5 (8%)	4 (7%)	6 (4%)	3 (7%)
Dry eye	11 (4%)	5 (8%)	1 (2%)	7 (12%)	9 (5%)	1 (2%)
Corneal oedema	10 (4%)	4 (7%)	3 (5%)	5 (9%)	0	0
Lacrimation increased	10 (4%)	0	2 (3%)	2 (3%)	2 (1%)	0
Anterior chamber cell	9 (4%)	6 (10%)	2 (3%)	1 (2%)	1 (0.6%)	0

	Arch100	Ladder100	Ladder 40	Ladder 10	Arch 0.5	Ladder 0.5
	N=248	N=59	N=62	N=58	N=167	N=41
Vision blurred	9 (4%)	5 (8%)	3 (5%)	8 (14%)	8 (5%)	3 (7.)
Eye irritation	8 (3%)	7 (12%)	7 (11%)	8 (14%)	8 (5%)	1 (2%)
Eyelid ptosis	8 (3%)	4 (7%)	2 (3%)	3 (5%)	0	0
Visual acuity reduced	7 (3%)	4 (7%)	4 (6%)	3 (5%)	1 (0.6%)	
Procedural pain	7 (3%)	2 (3%)	4 (6%)	1 (2%)	0	0
Retinal hemorrhage	7 (3%)	2 (3%)	4 (6%)	5 (9%)	2 (1%)	1 (2%)
Eye pruritus	7 (3%)	1 (2%)	1 (2%)	1 (2%)	2 (1%)	0
Conjunctivitis	7 (3%)	1 (2%)	0	1 (2%)	1 (0.6%)	0
Ecchymosis	7 (3%)	0	1 (2%)	0	0	0
Conjunctival erosion	6 (2%)	2 (3%)	2 (3%)	1 (2%)	0	0
Vitritis	6 (2%)	0	1 (2%)	0	0	0
Iris adhesions	6 (2%)				0	
Vital dye staining cornea present	6 (2%)				0	
Intraocular pressure increased	5 (2%)	4 (7%)	3 (5%)	6 (10%)	2 (1%)	2 (5%)
Cataract nuclear	5 (2%)	2 (3%)	3 (5%)	3 (5%)	1 (0.6%)	1 (2%)
Photophobia	5 (2%)	1 (2%)	4 (6%)	1 (2%)	3 (1.8%)	0
Conjunctival retraction	5 (2%)	1 (2%)	2 (3%)	0	0	0
Ocular discomfort	5 (2%)	1 (2%)	2 (3%)	1 (2%)	2 (1%)	0
Conjunctival disorder	5 (2%)				0	
Corneal dystrophy	5 (2%)				0	
Neovascular age-related macular degeneration	4 (2%)	4 (7%)	1 (2%)	2 (3%)	4 (2%)	2 (5%)
Visual impairment	4 (2%)	2 (3%)	1 (2%)	2 (3%)	3 (1.8%)	2 (5%)
Endophthalmitis	4 (2%)	1 (2%)	1 (2%)	1 (2%)	1 (0.6%)	0
Corneal abrasion	4 (2%)	1 (2%)	0	3 (5%)	2 (1%)	0
Intraocular pressure decreased	4 (2%)	0	3 (5%)	3 (5%)	1 (0.6%)	0
Cataract subcapsular	4 (2%)	0	1 (2%)	2 (3%)	2 (1%)	1 (2%)
Conjunctival cyst	4 (2%)	0	0	1 (2%)	0	0
Eyelid oedema	3 (1%)	3 (5%)	2 (3%)	1 (2%)	0	1 (2%)
Macular fibrosis	3 (1%)	2 (3%)	1 (2%)	0	1 (0.6%)	0
Iridocyclitis	3 (1%)	1 (2%)	0	3 (5%)	0	0
Cataract cortical	3 (1%)	0	2 (3%)	1 (2%)	1 (0.6%)	3 (7%)
Corneal striae	3 (1%)				0	
Device dislocation	3 (1%)				0	
Eye discharge	2 (1%)	3 (5%)	1 (2%)	2 (3%)	0	0
Vitreous disorder	2 (1%)	3 (5%)	0	1 (2%)	0	1 (2%)
Photopsia	2 (1%)	2 (3%)	0	2 (3%)	0	0
Diplopia	2 (1%)	1 (2%)	3 (5%)	3 (5%)	1 (0.6%)	1 (2%)
Drug hypersensitivity	2 (1%)	1 (2%)	1 (2%)	0	1 (0.6%)	0
Rhegmatogenous retinal detachment	2 (1%)	1 (2%)	1 (2%)	2 (3%)	0	0
Scleral hyperemia	2 (1%)	1 (2%)	1 (2%)	1 (2%)	0	0
Device deposit issue	2 (1%)	1 (2%)	0	0	0	0
Swelling of eyelid	2 (1%)	1 (2%)	0	1 (2%)	3 (1.8%)	0
Dry age-related macular degeneration	2 (1%)	0	3 (5%)	1 (2%)	2 (1%)	0
Ocular hypertension	2 (1%)	0	2 (3%)	2 (3%)	2 (1%)	1 (2%)
Retinal degeneration	2 (1%)	0	1 (2%)	0	1 (0.6%)	1 (2%)
Retinal tear	2 (1%)	0	1 (2%)	0	2 (1%)	0
Choroidal detachment	2 (1%)	0	0	3 (5%)	0	0
Hordeolum	2 (1%)	0	0	0	0	2 (5%)
Macular degeneration	2 (1%)	0	0	3 (5%)	0	1 (2%)

	Arch100	Ladder100	Ladder 40	Ladder 10	Arch 0.5	Ladder 0.5
	N=248	N=59	N=62	N=58	N=167	N=41
Chorioretinal folds	2 (1%)				0	
Detachment of retinal pigment epithelium	2 (1%)				2 (1%)	
Eyelid contusion	2 (1%)				0	
Foreign body in eye	2 (1%)				0	
Halo vision	2 (1%)				0	
Implant site discoloration	2 (1%)				0	
Lacrimation decreased	2 (1%)				1 (0.6%)	
Post procedural complication	2 (1%)				0	
Post procedural discomfort	2 (1%)				0	
Retinal disorder	2 (1%)				1 (0.6%)	
Scleral thinning	2 (1%)				0	
Telangiectasia	2 (1%)				1 (0.6%)	
Vitreous opacities	2 (1%)				1 (0.6%)	
Hyphema	1 (0.4%)	4 (7%)	1 (2%)	4 (7%)	0	0
Dermatochalasis	1 (0.4%)	2 (3%)	0	0	1 (0.6%)	1 (2%)
Altered visual depth perception	1 (0.4%)	1 (2%)	0	0	0	0
Episcleritis	1 (0.4%)	1 (2%)	0	0	0	0
Erythema of eyelid	1 (0.4%)	1 (2%)	0	1 (2%)	0	0
Eyelids pruritus	1 (0.4%)	1 (2%)	0	4 (7%)	0	0
Vitreous degeneration	1 (0.4%)	1 (2%)	0	1 (2%)	2 (1%)	0
Ocular hyperemia	1 (0.4%)	0	2 (3%)	3 (5%)	2 (1%)	1 (2%)
Chalazion	1 (0.4%)	0	1 (2%)	0	1 (0.6%)	0
Complication associated with device	1 (0.4%)	0	1 (2%)	1 (2%)	0	0
Conjunctival filtering bleb leak	1 (0.4%)	0	1 (2%)	0	0	0
Dermatitis contact	1 (0.4%)	0	1 (2%)	0	0	0
Device material opacification	1 (0.4%)	0	1 (2%)	0	0	0
Post procedural swelling	1 (0.4%)	0	1 (2%)	1 (2%)	0	0
Retinal pigment epithelial tear	1 (0.4%)	0	1 (2%)	0	0	1 (2%)
Optic atrophy	1 (0.4%)	0	0	2 (3%)	0	0
Retinal depigmentation	1 (0.4%)	0	0	1 (2%)	0	0
Subretinal fluid	1 (0.4%)	0	0	1 (2%)	1 (0.6%)	0
Trichiasis	1 (0.4%)	0	0	1 (2%)	0	0
Visual field defect	1 (0.4%)		1 (2%)	0		
Administration site discomfort	1 (0.4%)				0	
Amaurosis fugax	1 (0.4%)				0	
Anterior capsule contraction	1 (0.4%)				0	
Anterior chamber fibrin	1 (0.4%)				0	
Asthenopia	1 (0.4%)				0	
Atrophy of globe	1 (0.4%)				0	
Chorioretinal disorder	1 (0.4%)				0	
Choroidal effusion	1 (0.4%)				0	
Conjunctival granuloma	1 (0.4%)				0	
Conjunctival pigmentation	1 (0.4%)				0	
Conjunctivitis allergic	1 (0.4%)				1 (0.6%)	
Eye injury	1 (0.4%)				0	
Eyelid pain	1 (0.4%)				0	
Facial pain	1 (0.4%)				0	
Glare	1 (0.4%)				0	
Hyalosis asteroid	1 (0.4%)				0	
Implant site fibrosis	1 (0.4%)				0	

	Arch100	Ladder100	Ladder 40	Ladder 10	Arch 0.5	Ladder 0.5
	N=248	N=59	N=62	N=58	N=167	N=41
Implant site reaction	1 (0.4%)				0	
Macular hole	1 (0.4%)				0	
Medication error	1 (0.4%)				0	
Meibomian gland dysfunction	1 (0.4%)				0	
Myalgia	1 (0.4%)				0	
Necrotizing retinitis	1 (0.4%)				0	
Ocular vasculitis	1 (0.4%)				0	
Optic nerve sheath hemorrhage	1 (0.4%)				0	
Pterygium	1 (0.4%)				0	
Retinal artery embolism	1 (0.4%)				0	
Retinal infarction	1 (0.4%)				0	
Retinal oedema	1 (0.4%)				1 (0.6%)	
Scleral oedema	1 (0.4%)				0	
Subconjunctival cyst	1 (0.4%)				0	
Uveitis	1 (0.4%)				0	
Vitreoretinal traction syndrome	1 (0.4%)				0	
Vitreous adhesions	1 (0.4%)				0	
Wound dehiscence	1 (0.4%)				0	
Chorioretinal atrophy	0	1 (2%)	0	1 (2%)	1 (0.6%)	1 (2%)
Borderline glaucoma	0	0	1 (2%)	0	1 (0.6%)	1 (2%)
Choroidal neovascularization	0	0	1 (2%)	1 (2%)	2 (1%)	0
Dyschromatopsia	0	0	1 (2%)	0	1 (0.6%)	0
Eye infection	0	0	0	0	1 (0.6%)	1 (2%)
Eyelid cyst	0	0	0	1 (2%)	1 (0.6%)	0
Macular pigmentation	0	0	0	0	1 (0.6%)	1 (2%)
Maculopathy	0	0	0	1 (2%)	1 (0.6%)	0
Blister	0				1 (0.6%)	
Burning sensation	0				1 (0.6%)	
Charles Bonnet syndrome	0				1 (0.6%)	
Cyanopsia	0				1 (0.6%)	
Ear infection	0				1 (0.6%)	
Ectropion	0				1 (0.6%)	
Erythema	0				1 (0.6%)	
Eyelid retraction	0				1 (0.6%)	
Facial bones fracture	0				1 (0.6%)	
Optic disc hemorrhage	0				1 (0.6%)	
Periorbital swelling	0				1 (0.6%)	
VIth nerve paralysis	0				1 (0.6%)	
Pruritus		2 (3%)	2 (3%)	0		0
Periorbital Hemorrhage		1 (2%)	3 (5%)	1 (2%)		0
Sensation of Foreign Body		1 (2%)	2 (3%)	1 (2%)		0
Age-related macular degeneration		1 (2%)	1 (2%)	0		0
Metamorphopsia		1 (2%)	1 (2%)	1 (2%)		0
Conjunctival degeneration		1 (2%)	0	0		0
Corneal epithelium defect		1 (2%)	0	1 (2%)		0
Cyclitis		1 (2%)	0	0		0
Eyelid Margin Crusting		1 (2%)	0	0		0
Implant site oedema		1 (2%)	0	0		0
Incision site hemorrhage		1 (2%)	0	0		0
Iris atrophy		1 (2%)	0	0		0
Night Blindness		1 (2%)	0	0		0

	Arch100	Ladder100	Ladder 40	Ladder 10	Arch 0.5	Ladder 0.5
	N=248	N=59	N=62	N=58	N=167	N=41
Ophthalmoplegia		1 (2%)	0	0		0
Post procedural hemorrhage		1 (2%)	0	0		0
Retinal cyst		1 (2%)	0	0		0
Retinopathy Hypertensive		1 (2%)	0	0		0
Anterior chamber pigmentation		0	1 (2%)	0		0
Astigmatism		0	1 (2%)	0		0
Corneal irritation		0	1 (2%)	0		0
Corneal pigmentation		0	1 (2%)	0		0
Corneal Scar		0	1 (2%)	0		0
Dellen		0	1 (2%)	0		0
Diabetic retinopathy		0	1 (2%)	0		0
Implant site erythema		0	1 (2%)	2 (3%)		0
Injection site discomfort		0	1 (2%)	0		0
Pigment dispersion syndrome		0	1 (2%)	1 (2%)		0
Pupillary deformity		0	1 (2%)	0		0
Subretinal fibrosis		0	1 (2%)	0		0
Wound Hemorrhage		0	1 (2%)	0		0
Wound Secretion		0	1 (2%)	0		0
Abnormal sensation in the eye		0	0	1 (2%)		0
Arcus Lipoides		0	0	1 (2%)		0
Conjunctivitis bacterial		0	0	1 (2%)		0
Eye Hemorrhage		0	0	1 (2%)		0
Implant Site Hemorrhage		0	0	1 (2%)		0
Implant site pain		0	0	1 (2%)		0
Injection site pain		0	0	0		1 (2%)
Keratitis		0	0	1 (2%)		0
Macular dystrophy congenital		0	0	1 (2%)		0
Nictitating spasm		0	0	1 (2%)		0
Open angle glaucoma		0	0	1 (2%)		0
Photosensitivity reaction		0	0	1 (2%)		0
Retinopathy Proliferative		0	0	1 (2%)		0
Scleritis		0	0	1 (2%)		0
Tractional retinal detachment		0	0	1 (2%)		0

Laboratory Findings

Limited laboratory testing was included in the clinical trials. No clinically significant differences between groups were noted.

11. Key Review Issues Relevant to Evaluation of Risk

11.1 Endophthalmitis

Issue

The delivery device provides a pathway for microorganism to enter the eye and cause endophthalmitis. Endophthalmitis can result in loss of vision.

List of cases

Center/Patient ID-Age/Sex/Race		Adverse Event MedDRA Preferred Term	Treatment	Study Day of Onset	
(b) (6)	79/F/Black	Endophthalmitis	Port Delivery 10	5	Ladder
	70/M/White	Endophthalmitis	Port Delivery 100	57	Archway
	82/M/White	Endophthalmitis	Port Delivery 100	59	Archway
	75/M/White	Endophthalmitis	Port Delivery 100	61	Ladder
	68/M/White	Endophthalmitis	Port Delivery 100	161	Archway
	76/M/White	Endophthalmitis	Port Delivery 40	185	Ladder
	84/F/White	Endophthalmitis	Port Delivery 100	282	Archway
	84/F/White	2nd Endophthalmitis	Port Delivery 100	512	Archway
	69/F/White	Endophthalmitis	0.5 ranibizumab	542	Archway
	82/F/White	Endophthalmitis	Port Delivery 100	596	Ladder/Extension
	70/F/White	Endophthalmitis	Port Delivery 100	853	Ladder/Extension
	63/F/White	Endophthalmitis	Port Delivery 100	644	Monthly/Extension

Conclusion

There is a significant imbalance in the number of cases of endophthalmitis. In the controlled portion of the Archway and Ladder trials, there were 7 of 427 (1.6%) subjects reporting endophthalmitis in the PDS groups and 1 of 208 subjects (0.5%) reporting endophthalmitis in the monthly treatment group. In addition, there were two PDS subjects in the extension portion of the trials who developed endophthalmitis and one subject with endophthalmitis who developed endophthalmitis a second time. One patient initially enrolled in the monthly treatment and switched to the port delivery, subsequently developed endophthalmitis. Multiple ports were flushed with vancomycin as part of the treatment of the endophthalmitis.

11.2 Implant Dislocation

Issue

The implant can become dislocated and slip into the vitreous.

Assessment

Center/Patient ID-Age/Sex/Race		Adverse Event MedDRA Preferred Term		Study Day of Onset	Study
(b) (6)	78/M/White	Device dislocation	Port Delivery 100	168	Archway
	69/F/White	Device dislocation	Port Delivery 100	425	Archway
	60/F/White	Device dislocation	Port Delivery 100	510	Archway
	69/F/White	Device dislocation	Port Delivery 10/40	1113	Extension

Conclusion

Evaluation by the applicant into the root cause of the dislocations suggested that scleral incisions greater than the recommended length was the primary cause of later dislocations. Renewed emphasis in scleral incision size appears to have reduced the incidence of dislocations.

11.3 Conjunctival erosion/recession

Issue

Conjunctival erosion/recession

Assessment

The most frequent types of concomitant ocular procedure were conjunctival repair (11 patients [4.4%] in the PDS 100 mg/mL arm and no patients in the intravitreal arm). The most frequent indications for this procedure were conjunctival erosion (5 procedures in 4 patients) and conjunctival retraction (3 procedures in 2 patients).

Conclusion

Conjunctival erosion and/or recession needs to be monitored and potentially repaired because it increases the likelihood of endophthalmitis.

12. Drug Product Administration
Clinical Use Observation Report

The clinical use observational study evaluated the use of the IFN and RFN with integrated filter by HCPs. The IFN and RFN under evaluation were the final product configuration planned to be commercialized. The study was conducted in accordance with the clinical use observation process document (VAL-0206285, version 1.0) and the clinical study protocols GR40549 (PORTAL) and GR40550 (PAGODA) and their corresponding IFU (TEC-0124315, version 9.0).

The subjects of this clinical use observation were retina specialists who are qualified HCPs specialized in the medical and surgical treatment of retinal diseases, experienced in performing vitreoretinal surgeries and intravitreal injections, and previously trained on PDS procedures. The initial fill procedure was performed by retina specialists in a surgical environment with assistance from ophthalmic surgical nurses and circulating nurses. The refill-exchange procedure was performed by retina specialists in an office room environment with assistance from retina specialist assistants.

A total of 34 uses (13 for IFN and 21 for RFN) of the PDS needles were evaluated for correct physician performance. Eighteen physicians were assessed across the two procedures and four of these physicians performed both procedures. The clinical use observation assessed the task performance of HCPs using the PDS needles during the two procedures. The surgical device liaisons (SDL) observed the procedures and recorded the data on checklists.

One of the participants (b) (6) depressed the plunger of the syringe quickly (< 5 seconds), which led to the introduction of micro bubbles in the implant. This was identified during inspection and the participant used a second set successfully to complete the procedure without the presence of any bubbles. The instructions include explicit steps that indicate the implant should be filled slowly over 5 – 10 seconds. They also indicate that the syringe, IFN hub and filled implant should be inspected for air before use. This observation did not affect patient safety or lead to any adverse events.

For the Task 2.7.1., one participant (b) (6) did not use the standard luer lock syringe but instead used a tapered syringe. However, the participant was successfully able to perform and complete the procedure. The instructions include the use of a luer lock syringe for the procedure. This was pointed out to the site and they acknowledged that the instructions were clear. This did not affect patient safety or lead to any adverse events.

One participant (b) (6) noticed improved visibility in targeting the septum with a thinner profile of the commercial RFN.

Conclusion
On the basis of the observation results, only minor errors were noted with the use of the devices and instructions.

13. Human Factors Study

Genentech's intent in performing HF analysis and use-related risk management is to ensure that the PDS can be used in a way that does not pose unacceptable use-related harms to patients or users. A Use Related Risk Analysis (URRA) was conducted to systematically identify and assess risks related to potential use errors and their impact on performance and safety. The risk analysis considered intended use and reasonably foreseeable misuse.

The URRA activities included:

- A hazard assessment was performed by a cross-functional team including clinical/ medical experts to evaluate and rate harm severity for each potential harm which could result from use error or reasonably foreseeable misuse.
- A hierarchical task analysis was performed to identify and analyze individual tasks required to use the product as intended.
- A Failure Modes and Effects Analysis (FMEA) was performed in conformance with the normative requirements of ISO14971 Medical Devices – Application of risk management to medical devices to analyze the potential use errors associated for each task and the potential for hazardous situations and harm to occur.
- The severity of harm and likelihood of the harm were identified for these errors. Known issues identified from clinical complaint data, usability studies and post-market experience on similar products, and available information from publicly available sources, including the FDA MAUDE database and published literature were also reviewed and incorporated into the risk analysis as appropriate.

A task analysis was created to identify and describe the individual tasks required to use the product as intended. Risk analysis was performed to determine task criticality.

Task criticality definitions

Criticality	Description
Essential Task (E)	Tasks required to perform the initial fill, implant insertion, refill-exchange and implant removal procedures.
Safety Critical Task (SC)	Tasks for which use errors would have a reasonably foreseeable potential for clinical impact/harm (severity 6 or greater, on a scale of 2 to 10).

Severity of potential harm rating criteria

Score	Category	Definition
10	Catastrophic	Effects may cause serious adverse health consequences, permanent disability, or death
8	Critical	Effects may cause a significant impact to patient health (e.g. temporary or medically reversible health problem or disability)
6	Major	Effects are noticeable by user and may make product unusable; requires medical intervention
4	Moderate	Effects are noticeable by user and may make product difficult to use; does not require any medical intervention

2	Minor/ Negligible	Effects will have negligible to no impact to patient health

Likelihood of potential harm rating criteria

Score	Category	Qualitative criteria	Occurrence of Harm per Million Exposure Opportunities (%)
10	Very High	Certain to occur routinely	> 6210 (>0.61%) / >6.1 in 1,000
8	High	Occurs frequently	≤ 6210 > 1350 (≤0.61% > 0.135%) / >1.35 in 1,000
6	Moderate	Occurs occasionally	≤ 1350 > 233 (≤0.135% > 0.023%) / >2.3 in 10,000
4	Low	Has not occurred often	≤ 233 > 3.4 (≤0.023% > 0.0034%) / >3.4 in 1,000,000
2	Remote	Not expected to occur	≤ 3.4 (≤0.0034%) / 3.4 or less in 1,000,000, or less

The probability of occurrence was calculated considering the probability of an error causing the user to be exposed to a hazardous situation combined with the probability of the hazardous situation leading to harm.

RISK EVALUATION

The magnitude of the resultant use-related risks is represented by a primary risk number (PRN). The PRN is a number calculated as the product of the rated severity of harm and rated likelihood of the harm occurring and is used as the basis for risk evaluation.

Primary risk number matrix

PRN = severity x probability of occurrence

		Probability of Occurrence				
		2	4	6	8	10
Severity	10	20	40	60	80	100
	8	16	32	48	64	80
	6	12	24	36	48	60
	4	8	16	24	32	40
	2	4	8	12	16	20

40-100	High: Require Risk Control Action(s)
16-36	Medium: risk control actions must be investigated to determine if risk can be reduced
4-12	Low: no further risk control actions are required

Reviewer's Comments: *The methodology that was employed is a standardized methodology recommended by the Agency, however, there is no requirement to provide a justification for the assigned values. As described below, there is reason to question the assigned values.*

Essential and safety critical tasks, use errors, potential harms and severities, and risk control measures

Reviewer's Comments: *As identified in yellow highlight below, this reviewer does not agree that the identified use errors would necessarily lead to the listed Potential Harms and Severities.*

Sub Task ID	Sub Task Description	Criticality	Use Errors	Potential Harms and Severities
1.2 1	Store ITA carton at room temperature	SC	• User stores ITA carton at wrong storage temperature and uses product that is stored improperly	Intraocular inflammation (8), increased IOP (6), conjunctival erosion (6), disease progression (6)
1.4 2	Check expiry date on the ranibizumab vial-IFN kit/ IFN cartons (note: expiry date can be found on the cartons, ranibizumab vial label, or IFN sterile barrier system)	SC	• User does not check the ranibizumab Vial-IFN Kit / ranibizumab vial expiry date and uses an expired product • User does not correctly read the ranibizumab Vial-IFN Kit / ranibizumab vial expiry date, and uses an expired product.	Decreased vision: seeing single or multiple floaters in visual field (4), disease progression (6), intraocular inflammation (6), immunogenicity: systemic (6), endophthalmitis (8), conjunctivitis (6), keratitis (6)
2.7 3	Remove air from syringe	SC	• User does not remove air bubbles from syringe • User over-primes syringe • User contacts RFN	Disease progression (6), conjunctival inflammation (4), pain (4), cut (4), inflammation (4)
2.7.4	Adjust dose	E & SC	• User over-primes syringe	Disease progression (6)
2.7.5	Inspect syringe and RFN for air bubbles	SC	• User does not inspect for air bubbles • User does not identify air bubbles in syringe or needle hub	Disease progression (6)
2.8 1	Stabilize the globe	SC	• User does not stabilize the globe	Cataract (8), disease progression (6)
2.8 2	Orient the RFN perpendicular to the globe	SC	• User waits too long to use primed syringe and RFN to refill implant • User contacts RFN • User does not orient refill needle perpendicular to globe and damages needle or needle is not fully in implant	Disease progression (6), pain (4), retinal detachment (8), cataract (8), intraocular inflammation (8), increased IOP (6), decreased vision: seeing single or multiple floaters in visual field (4), intraocular inflammation (6), immunogenicity: systemic (6), inflammation (4), conjunctival abrasion or hemorrhage (6), conjunctival erosion (6), conjunctival inflammation (4)

Sub Task ID	Sub Task Description	Criticality	Use Errors	Potential Harms and Severities
3.6.5	Align the contoured tips of the explant tool with the long axis of the implant flange and perpendicular to the globe	SC	• User grasps Implant with a incorrectly oriented explant tool	Retinal detachment (8), cataract (8)
3.6.6	Grasp underneath the long axis of the implant flange with the explant tool tips	E & SC	• User contacts lens • User uses other tools used to explant implant • User has difficulty grasping the implant with the explant tool	Retinal detachment (8), cataract (8), pain (4)
3.6.10	Suture conjunctiva	SC	• User does not completely close the conjunctiva	Vitreous prolapse (8), Endophthalmitis (8)
3.7.1	Ensure all packaging and materials have been disposed into appropriate waste containers	SC	• User does not appropriately dispose of materials and devices	Endophthalmitis (8)

Reviewer's Comments: *Failure to close the conjunctiva is likely to increase the incidence of endophthalmitis, but it was not listed as a potential harm. Failing to ensure that all packaging and materials have been disposed into the appropriate waste containers would not lead to endophthalmitis. Other improbable events are identified by yellow highlighting.*

SUMMARY OF PRELIMINARY ANALYSES AND EVALUATIONS

Formative usability studies have been conducted throughout development to inform the PDS design, IFU, and training. The results from each study have been incorporated into the product design and the risk analysis. Table 10 lists an overview of all user studies conducted to date. Many of these studies utilized the (b) (4) configuration. These studies also tested ancillary devices, the IFU, and training. Discussion of these studies is necessary to fully detail the design evolution and evaluation of the system. Portions of the studies that focused on the (b) (4) will not be discussed as the (b) (4) configuration is outside the scope of this report.

Table 10. Overview of PDS formative studies

Formative study	Study Type	Study Sample Size	PDS Procedures Evaluated
Study 1 (Section 6.1.1)	Simulated use, Design evaluation (insertion tool)	4 internal ophthalmologists*	Initial fill and implant
Study 2 (Section 6.1.2)	Simulated use, Design evaluation (insertion tool)	5 vitreoretinal surgeons	Initial fill and implant
Study 3 (Section 6.1.3)	Simulated use, Implant force measurement	4 ophthalmic surgeons	Initial fill and implant Implant removal
Study 4 (Section 6.1.4)	Simulated use, Design evaluation (IT packaging)	3 internal ophthalmologists*	Implant removal
Study 5 (Section 6.1.5)	Anthropometric (insertion tool)	30 internal employees	Initial fill and implant
Study 6 (Section 6.1.6)	Simulated use	9 vitreoretinal surgeons 5 retinal specialists	Initial fill and implant
Study 7 (Section 6.2.1)	Simulated use	6 scrub nurses 8 retina specialists with retinal surgical training 8 retina specialists with injection experience	Initial fill and implant Refill-exchange Implant removal
Study 8 (Section 6.2.2)	Simulated use	8 retina specialists with retinal surgical training	Initial fill and implant Implant removal
Study 9 (Section 6.2.3)	Simulated use	8 retina specialists with retinal surgical training	Initial fill and implant Refill-exchange Implant removal
Study 10 (Section 6.2.4)	Simulated use	8 retina specialists with retinal surgical training 4 retina specialists with injection experience • ophthalmic nurses • retina specialist assistants	Initial fill and implant Refill-exchange Implant removal
Study 11 (Section 6.2.5)	Simulated use	6 ophthalmic nurses 5 retina specialist assistants	Initial fill and implant Refill-exchange

*internal ophthalmologists are Genentech clinicians

DETAILS OF HUMAN FACTORS VALIDATION TESTING
A simulated-use HF validation study was conducted. The study was executed by (b) (4) . The study was conducted to demonstrate that PDS (including ranibizumab 100mg/mL vial, ITA, IFN, RFN, ET), along with its packaging, labeling, training, and IFUs, can be used by the intended users in the intended use environments without patterns of serious use errors or problems.

This study was a design validation stage activity performed in accordance with the Design Validation Master Plan (Genentech ref: VAL-0201314). The study design and procedures followed can be found in the approved study protocol (Genentech ref: VAL-0201150).

VALIDATION APPROACH AND RATIONALE
Simulated-use testing with representative users was employed in the HF validation study to evaluate the PDS. This study type was appropriate for this context because a simulated setting allowed the study moderator and observer to view each interaction in real time. Since users were asked to perform tasks in the same order as expected in a real-world setting, a simulated- use test provided insights into potential difficulties and areas of confusion over the entire course of use, rather than in segments. By contrast, alternative testing approaches (e.g., real-world use) would have required participants to complete tasks on real human eyes. As a result, the repeated testing with real patients could have presented unnecessary risks to the patients and introduced confounding variation into the test results. Hence, the conditions of a simulated use study were deemed to be sufficiently realistic as the results represent aspects of actual product use.

Reviewer's Comments: *Strongly disagree that simulated-use is adequately representative of the real-world setting or that a real world setting would have presented unnecessary risk to patients. The participants repeatedly made errors which they attributed to differences between the testing environment and the real world. In addition, there are procedural steps and availability of equipment in a real world setting, including the patient prep and positioning which are not accounted for in this testing situation.*

STUDY ENVIRONMENT
The HF validation study simulated the intended use environments as closely as is reasonably practicable. All study sessions were conducted in standard market research facilities. The interview room consisted of two set-ups – surgical setting and clinic setting. The interview room was set up to allow participants to use the system independently and in as natural a manner as possible. Participants were able to sit or stand depending on their preference and typical practice. Suitable table surfaces simulating the sterile field provided access to devices. All needed surgical tools and magnifying aids were provided.

The test room was illuminated by typical incandescent and/or overhead fluorescent lights common in a surgical/clinical environment. The test room was relatively quiet; however, there were occasional acoustic distractions. These noises were not controlled to represent the actual use environment. The study environments were under climate-controlled conditions representative of typical surgical/clinical environments.

Due to COVID-19, participants were screened for symptoms of and exposure to COVID-19 during the recruiting process. Participants received a copy of the (b) (4) COVID-19 Safety Precautions flyer upon arrival (Genentech ref: VAL-0201150). Masks were required for all study personnel and participants. Additionally, precautions were taken to allow for proper social distancing as often as possible. There were some study tasks for which a moderator passed materials to participants or assisted in setting up materials, which required them to be closer than six feet. Lastly, a turnaround time between sessions was included to account for COVID-19 control and disinfection measures.

STUDY PARTICIPANTS
A total of 53 users participated in this study. The sample size breakdown for each user group was 23 retina specialists/ophthalmologists, 15 ophthalmic surgical nurses/technicians, and 15 retina specialist assistants. For the retina specialists, three separate groups were created to ensure that 15 of the 23 participants completed each PDS procedure.

The 15 sample size was selected based on the FDA Human Factors Guidance (2016), "Applying Human Factors and Usability Engineering to Medical Devices" and AAMI/ANSI-HE- 75:2009 part 9.2. During the study no statistical hypothesis testing was performed.

Participants were assigned an alphanumeric ID.

Group	Use Environment	Number of Study Participants	Procedures Assessed	Participant Identifier
Retina Specialists / Ophthalmologists	Surgical	8	• Initial fill and implant • Implant removal	RS
	Clinic	8	• Refill-exchange	RC
	Both (surgical and clinic)	7	• Initial fill and implant • Refill-exchange • Implant removal	RB
Ophthalmic Surgical Nurses / Technicians (scrub/circulating)	Surgical	15	• Initial fill and implant • Implant removal	S
Retina Specialist Assistants	Clinic	15	• Refill-exchange	A

Results with scores less than 90%:

Performance results for retina specialists - initial fill and implant

Type	Intended Task	Success	Difficulty	Use Error	N/A	Correct Rate %[1]
OBS	1.9.3 Remove air from syringe	11	1	3	0	12/15, 80%
OBS	1.9.4 Inspect syringe and IFN for air bubbles	12	1	2	0	13/15, 86%
OBS	1.10.2 Align syringe luer with luer collar slot in IT carrier	10	0	5	0	10/15, 66%
OBS	1.10.4 Depress plunger slowly to inject the contents of the syringe into the implant under microscope	10	1	4	0	11/15, 73%
OBS	1.10.5 Inspect the implant for air bubbles under the microscope	11	0	4	0	11/15, 73%
OBS	1.10.10 Set IT handle with filled implant aside	13	0	2	0	13/15, 86%
OBS	1.11.3 Perform scleral incision	13	0	2	0	13/15, 86%
OBS	1.11.8 Stabilize the globe	10	3	2	0	13/15, 86%

Performance results for surgical nurse/techs - initial fill and implant

Type	Intended Task	Success	Difficulty	Use Error	N/A	Correct Rate %[2]
OBS	1.4.5 Remove contents from ranibizumab vial-IFN kit carton	13	0	2	0	13/15, 86%
OBS	1.4.17 Remove IFN from SBS using aseptic technique and place onto sterile field	11	0	4	0	11/15, 73%
OBS	1.4.18 Remove ITA with implant from SBS using aseptic technique and place onto sterile field	11	1	3	0	12/15, 80%
OBS	1.8.2 Disinfect vial septum with alcohol pad	11	0	4	0	11/15, 73%
OBS	1.8.3 Screw filter needle onto syringe	10	0	5	0	10/15, 66%
OBS	1.8.5 Withdraw all the drug product from vial through filter needle into syringe	10	1	4	0	11/15, 73%
KBA	1.12.3. According to the instructions, can you locate the information to be filled in the patient implant card?	7	0	8	0	7/15, 46%

Performance results for surgical nurse/techs - initial fill and implant

Type	Intended Task	Success	Difficulty	Use Erro	N/A	Correct Rate %[2]
OBS	1.4.5 Remove contents from ranibizumab vial-IFN kit carton	13	0	2	0	13/15, 86%
OBS	1.4.17 Remove IFN from SBS using aseptic technique and place onto sterile field	11	0	4	0	11/15, 73%
OBS	2.4.12 Remove RFN from SBS using aseptic technique and place onto sterile field	3	0	1	11	3/4, 75%
OBS	2.6.3 Screw filter needle into syringe	12	0	3	0	12/15, 80%
OBS	2.6.5 Withdraw all the drug product from vial through filter needle into syringe	13	0	2	0	13/15, 86%
OBS	2.7.3 Remove air from syringe	11	0	4	0	11/15, 73%
OBS	2.7.5 Inspect syringe and RFN for air bubbles	12	0	3	0	12/15, 80%
OBS	2.8.1 Stabilize the globe	13	0	2	0	13/15, 86%
OBS	2.4.5 Remove contents from ranibizumab vial carton (vial and USPI)	11	0	4	0	11/15, 73%
OBS	2.4.7 Remove contents from RFN carton (SBS)	11	0	4	0	11/15, 73%
OBS	2.4.12 Remove RFN from SBS using aseptic technique and place onto sterile field	0	1	14	0	1/15, 7%

Based on results of the HF validation study, minor modifications were made to the IFU in an effort to provide the user with additional opportunities to perform tasks correctly. The updates include:

- Initial fill and implant IFU:
  - In the Syringe Preparation and Initial Implant Fill section of the IFU, under *Step 5 - Load syringe into the carrier* instruction was updated to clarify that failure to align the syringe correctly can damage the needle.
  - On the implant card in the IFU, the "(b) (4)" was updated to "Implant lot number" to provide clarity.
- Implant removal IFU:
  - In the device description section of the IFU, Figure 2 was updated to indicate location of the "finger grips" on the tool.

Additional updates were made to some sections in the IFUs; however, those sections were either not part of the HF validation study (as they were standard surgical procedures, and not device use tasks) or were related to clinical information based on safety data from clinical studies. The updates made to the IFU are intended to emphasize information that is already included and to add redundancies that will increase saliency of critical information. These changes are expected to have a positive impact on usability based on adherence to HF principles, and no instructions

have been substantially changed or removed. Thus, the results of the study are valid in regards to evaluation of the device user interface, and additional validation of these minor updates is not necessary.

HUMAN FACTORS VALIDATION STUDY SPONSOR's CONCLUSION

Overall, results of the HF validation study demonstrate that users safely and correctly used the PDS system without safety-critical use errors that could be further controlled through design. Participants in the HF validation study completed simulated-use tasks and knowledge-based assessments in order to evaluate the usability of the PDS system. Results from the study were successful with overall correct rate across user groups at 94%. Root cause analysis of observed use error and difficulties found that the current interfaces are sufficient in communicating safety critical information. Further modifications to the user interface would not be likely to reduce the rate of the performance issues that were observed.

The only notable pattern of use errors to emerge occurred in the retina specialist assistant group. These participants to maintain aseptic technique when preparing the sterile components. Debriefing feedback indicated that there is a lack of knowledge among retina specialist assistants with regard to the meaning of aseptic technique and this is largely influenced by negative transfer from their current work environments. Retina specialist assistants typically prepare intravitreal injections using a "clean technique." That is, they avoid touching surfaces of the device that will contact the patient or medication, but do not perform the task aseptically.

Design controls cannot prevent the misapplication of aseptic technique; however, the instructions and packaging appropriately indicate that aseptic technique should be used and the packaging includes symbols to indicate sterile contents when appropriate. Finally, because the retina specialist assistants used "clean technique," none of them had aseptic breaches with a high potential for risk of contamination. That is, none of the retina specialist assistants touched the luer points on the syringes, filter needle, or RFN, nor did they touch the actual needle on the filter needle or RFN.

Overall, the results indicate that users will be able to operate the PDS devices safely and effectively under the intended use conditions in the intended use environment without patterns of preventable harm.

Reviewer's Comments: *The Human Factor's study identified problems with the initial placement and maintenance of the components in a sterile field. This is a critical factor potentially leading to an increase in cases of endophthalmitis. The speed at which the injection was performed and the assessment of bubbles in the implant also raises potential concern because it is identified as potentially leading to disease progression. The scientific basis to conclude that it leads to disease progression remains questionable.*

It is strongly recommended that Human Factor's studies for surgically implanted products be conducted in real world settings and that the risks assigned include accurate plausibility.

14. Plans for Pediatric Drug Development

By definition, neovascular age-related macular degeneration does not occur in children. It occurs in adults over the age of 50.

15. Pregnancy and Lactation

Neovascular age-related macular degeneration rarely occurs in women while they are likely to be pregnant or lactating.

16. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections

Studies appear to have been conducted in accordance with good clinical practice guidance.

17. Advisory Committee Summary

An Advisory Committee Meeting was not scheduled during the review of this application. Ranibizumab administered intravitreally has been approved and marketed for over 15 years. The safety issues identified with the Port Delivery are similar to safety issues known to occur with IOP filtering valves.

18. DEMPA Review

The results of the HF validation study demonstrated several use errors/close calls/use difficulties with critical tasks that may result in harm. However, the Division of Ophthalmology requested labeling changes in an information request on July 16, 2021, to further mitigate the identified risks. The Applicant responded with additional information and proposed labeling changes on July 22, 2021, and we find their response to be acceptable.

Furthermore, our evaluation of the proposed user interface, proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 11 for the Division and Table A for the Applicant. We ask that the Division convey Table A in its entirety to the Applicant. In addition, we provide our recommendations for the Applicant related to the HF validation study in section 4.1 below. We ask that the Division convey Table A in its entirety to the Applicant so that recommendations are implemented prior to approval of this BLA 761197.

The Division of Ophthalmology acknowledge the recommendations from DEMPA, but disagrees with several of the recommendations and notes that some of the recommendations are not consistent with the Office of Drug Safety's recommendations. Specific comments are listed below.

Table 11: Identified Issues and Recommendations from DMEPA				Ophthalmology Conclusion
	Identified Issue	**Rationale for Concern**	**Recommendation**	
Prescribing Information- General Issues				
1	The non-proprietary name suffix is denoted by the placeholder "-xxxx"		Replace "-xxxx" with the conditionally acceptable non-proprietary name suffix when it is determined.	As described in the memorandum from the Office of Surveillance and Epidemiology, a suffice will not be included. The current established name will be retained.
Highlights of Prescribing Information: Dosage and Administration				
1	There is no direction to follow the Initial Fill Implant Procedure IFU and the Implant Removal Procedure IFU documents while preparing to administer the product.	Clear direction for the user to follow the appropriate IFU is necessary to mitigate the risk of preparation and administration errors.	In the *Dosage and Administration* section of the Highlights, add directions for the user to use the Initial Fill Implant Procedure IFU and the Implant Removal Procedure IFU when preparing to administer or remove the implant.	Disagree. There is not sufficient space to present a meaningful description of the Dosage and Administration in the Highlights.
	The incorrect concentration is displayed in the second bullet point e.g., (0.02 mL of 100 mg/mL solution).	The correct product concentration should be displayed for dosing calculations and administration in order to mitigate the risk of dosing error.	Revise "100 mg/mL" to "10 mg/0.1 mL" so that the second bullet point reads: "...(0.02 mL of 10 mg/0.1 mL solution)..."	Disagree. Describing this product as 10mg/0.1mL will cause confusion with the intravitreal injection product which is 10mg/mL.
Highlights of Prescribing Information: Dosage Forms and Strength				
3.	The strength dose not match the strength in the rest of the PI	The correct strength should be displayed in order to mitigate	In the *Dosage Forms and Strengths* section of the highlights, change "100 mg/1 mL" to "10 mg/ 0.1 mL".	Disagree. Describing this product as 10mg/0.1mL will cause confusion with the intravitreal injection

	and the container label and carton labeling.	the risk for dosing errors.		product which is 10mg/mL.
Full Prescribing Information: Dosage and Administration				
	Section 2.1, (b) (4)		Revise the title of Section 2.1 to *General Information*.	Corrected.
	The sections within Section 2 of the FPI are not in correct numerical order.		Correct the numbering of the sections within Section 2 of the FPI.	Corrected.

Table A: Identified Issues and Recommendations for Genentech, Inc. (entire table to be conveyed to Applicant)				**Ophthalmology Conclusion**
	Identified Issue	**Rationale for Concern**	**Recommendation**	
Training				
	The summative validation testing results revealed that the Retina Specialists/Ophthal mologists, Ophthalmic Surgical Nurses/Technicians, and Retina Specialist Assistants experienced serious use errors on observational task performance and labeling comprehension failures and close calls associated with critical tasks.	These failures would have impacted the PDS system use-safety and potentially cause serious clinical harm to the patient in a "real-world" setting.	We recommend using the findings of the root cause analysis to further develop your training materials, train-the-trainer materials, hands-on practices, and certification (if applicable) program specific to each distinct user group. For example, consider including information on proper use of the tools provided (such as where to grasp) to your training material.	The study was flawed because it was in an artificial setting and the surgical team knew that they were administering the product to a real patient.
Instructions for Use (IFU) (Initial Fill Implant Procedure/ Implant Removal Procedure) and Medication Guide				
	The non-proprietary name suffix is denoted by the placeholder "-xxxx".		Replace "-xxxx" with the conditionally acceptable non-	As described in the

			proprietary name suffix when it is determined.	memorandum from the Office of Surveillance and Epidemiology, a suffice will not be included. The current established name will be retained.
Container Label, Carton Labeling and Packaging				
	The format for the expiration date is not defined.	Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.	Agree. Labeling has been revised.
	The non-proprietary name suffix is denoted by the placeholder "-xxxx"		Replace "-xxxx" with the conditionally acceptable non-proprietary name suffix when it is determined.	As described in the memorandum from the Office of

				Surveillance and Epidemiology, a suffice will not be included. The current established name will be retained.
	The net quantity of drug product contained in the vial is not displayed on the container label, carton labeling or the packaging (kit carton).	The net quantity of drug product contained in the vial is not displayed on the appropriate labeling.	Add the net quantity to the PDP of the container label, carton labeling and the packaging (kit carton).	A minimum quantity will be listed on the vial.
Carton Labeling and Packaging (kit carton)				
	We note that the carton labeling and packaging (kit carton) do not include a machine-readable 2D data matrix barcode.	In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.[1] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017,	Add the machine-readable 2D data matrix barcode on the carton labeling and packaging.	Agree. Labeling has been revised.

[1] Draft Guidance: Product Identifiers Under the Drug Supply Chain Security Act-Questions and Answers. Food and Drug Administration. 2018. Available from https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

		and November 27, 2018, respectively.		

19. Additional Clinical Trial Information

19.1 Archway Trial

	Site	Principal Investigator	Ranibizumab Port 100 mg/mL	Ranibizumab 0.5 mg	Total
			251	167	418
1	535279	Clark, William	12	10	22
2	405751	Khanani, Arshad	11	8	19
3	16103	Mittra, Robert	9	7	16
4	435133	Jhaveri, Chirag	10	4	14
5	289567	Brooks, H. Logan	10	3	13
6	14254	Pieramici, Dante	10	3	13
7	13897	Marcus, Dennis	7	5	12
8	13953	Awh, Carl C.	3	10	10
9	285706	Wykoff, Charles C.	8	2	10
10	295425	Eichenbaum, David	6	4	10
11	429223	Suan, Eric	7	3	10
12	20339	Wagner, Alan	6	4	10
13	291484	Kwong, Henry	7	2	9
14	437380	Williams, Patrick	4	5	9
15	487028	Adam, Murtaza	4	5	9
16	535286	Graff, Jordan	6	3	9
17	14609	Regillo, Carl	6	3	9
18	19948	Gupta, Sunil	5	4	9
19	280688	Chang, Margaret	6	2	8
20	10010	Antoszyk, Andrew	6	2	8
21	17521	Campochiaro, Peter	7	1	8
22	437072	Howard, James	3	4	7
23	536490	Batlle, Ivan	5	2	7
24	10015	Dreyer, Richard	3	4	7
25	18328	Suner, Ivan	4	3	7
26	18955	Kitchens, John	7	0	7
27	13995	Brown, David M	4	2	6
28	433905	Wolfe, Jeremy	1	5	6
29	435482	Dhoot, Dilsher	2	4	6
30	19968	Moore, Jeffrey	3	3	6
31	22667	Miller, Daniel	4	2	6
32	282173	Callanan, David	2	3	5
33	291466	Goff, Mitchell	4	1	5
34	305123	Wells, John A.	2	3	5
35	489111	Engstrom, Robert	3	2	5
36	23662	Stoltz, Robert	3	2	5
37	297467	Nielsen, Jared	3	1	4
38	428002	Burgess, Stuart	2	2	4
39	437099	Huddleston, Stephen	3	1	4

	Site	Principal Investigator	Ranibizumab Port 100 mg/mL	Ranibizumab 0.5 mg	Total
40	438171	Lai, Michael	2	2	4
41	13956	Thompson, John	1	3	4
42	19299	Feiner, Leonard	1	3	4
43	20422	Holekamp, Nancy	2	2	4
44	13430	Aaberg Jr., Thomas	1	2	3
45	273244	Higgins, Patrick	1	2	3
46	432325	Haug, Sara	3	0	3
47	436947	Ohr, Matthew	2	1	3
48	528890	Phelps, Brian	3	0	3
49	13872	Michels, Mark	3	0	3
50	16230	Chaudhry, Nauman	1	2	3
51	22247	Chen, Sanford	2	1	3
52	272841	London, Nikolas	0	2	2
53	428857	Wirthlin, Robert	0	2	2
54	436204	Crews, Kent	2	0	2
55	452904	Hong, Bryan	1	1	2
56	468365	Sheth, Veeral	2	0	2
57	476507	Schadlu, Ramin	2	0	2
58	484098	Sigler, Eric	2	0	2
59	10019	Johnson, Robert	0	2	2
60	12253	Bhisitkul, Robert	2	0	2
61	13525	Singer, Michael	0	2	2
62	19320	Wieland, Mark	1	1	2
63	19391	Baker, Carl	1	1	2
64	289677	Walker, Joseph	0	1	1
65	299283	Barakat, Mark	1	0	1
66	388313	Wong, Robert	0	1	1
67	436209	Mccannel, Colin	0	1	1
68	437444	Brown, Jamin	1	0	1
69	441358	Goldberg, Roger	1	0	1
70	484790	Rachitskaya, Aleksandra	0	1	1
71	10018	Heier, Jeffrey	1	0	1
72	13251	Boyer, David	0	1	1
73	13395	Ferrone, Philip	1	0	1
74	14199	Schneiderman, Todd	1	0	1
75	18952	Blinder, Kevin	0	1	1
76	19054	Pollack, John	0	1	1
77	20253	Tabassian, Ali	1	0	1
78	22665	Hershberger, Vrinda	1	0	1

19.2 Ladder Trial

			10 mg/mL	40 mg/mL	100 mg/mL	0.5 mg	Total
	Site	Investigator	59	62	63	41	225
1	10010	Antoszk, Andrew	1	0	1	1	3
2	10015	Dreyer, Richard	3	2	3	2	10
3	10019	Johnson, Robert	0	3	0	0	3
4	12253	Bhisitkul, Robert	0	1	1	0	2
5	12609	Freeman, William	1	1	2	3	7
6	13430	Aaberg Jr., Thomas	1	2	2	0	5
7	13466	Berger, Brian	0	2	2	2	6
8	13525	Singer, Michael	1	0	2	0	3
9	13897	Marcus, Dennis	3	1	0	1	5
10	13953	Awh, Carl C.	1	2	3	2	8
11	13956	Thompson, John	1	1	2	0	4
12	13995	Brown, David M.	1	0	1	0	2
13	14008	Katz, Randy	1	1	0	0	2
14	14132	Clark, W. Lloyd	0	1	3	0	4
15	14254	Pieramici, Dante	2	1	1	1	5
16	14609	Regillo, Carl	1	2	0	2	5
17	16103	Mittra, Robert	1	3	1	1	6
18	16727	Gordon, Alan	3	2	0	0	5
19	17521	Campochiaro, Peter	1	0	2	1	4
20	17798	Dugel, Pravin	1	0	1	0	2
21	18328	Suner, Ivan	0	1	1	2	4
22	18955	Kitchens, John	0	1	0	2	3
23	19054	Pollack, John	2	2	1	0	5
24	19320	Wieland, Mark	4	1	0	2	7
25	19391	Baker, Carl	0	1	1	0	2
26	19948	Gupta, Sunil	0	1	2	1	4
27	20339	Wagner, Alan	1	1	0	0	2
28	22247	Chen, Sanford	5	1	4	2	12
29	22264	Rose, Steven	1	0	0	0	1
30	22667	Miller, Daniel	2	4	2	0	8
31	23628	Mccabe, Frank	0	0	1	0	1
32	273167	Calzada, Jorge	0	0	1	0	1
33	273244	Higgins, Patrick	2	0	3	1	6
34	280688	Chang, Margaret	1	1	1	2	5
35	280698	Chittum, Mark	1	0	0	0	1
36	282173	Callanan, David	2	4	2	5	13
37	289677	Walker, Joseph	1	1	0	0	2
38	295425	Eichenbaum, David	4	3	1	0	8
39	297467	Nielsen, Jared	0	0	1	0	1

			10 mg/mL	40 mg/mL	100 mg/mL	0.5 mg	Total
	Site	Investigator	59	62	63	41	225
40	405751	Khanani, Arshad	2	2	3	2	9
41	436209	Mccannel, Colin	1	1	2	0	4
42	436560	Zilis, John	3	2	0	0	5
43	437072	Howard, James	0	3	4	2	9
44	437389	Lauer, Andreas	2	2	0	1	5
45	438171	Lai, Michael	0	1	1	0	2
46	469761	Engstrom, Robert	2	2	2	1	7
47	484790	Rachitskaya, Aleksandra	0	0	0	2	2
48	489631	Graff, Jordan	0	2	3	0	5

20. Name and Package Insert

A memorandum from Lubna Merchant, M.S., PharmD., Deputy Director, OMEPRM Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research through Gerald Dal Pan, M.D., M.H.S., Director, Office of Surveillance and Epidemiology Center for Drug Evaluation and Research establishes that the established name of the product will not be changed. As described in the memorandum, "We noted above that this change could also be managed under a supplement to the current BLA, which would not have resulted in a change to the proper name under the approach to nonproprietary naming described in the final guidance. As noted in the final naming guidance, distinguishing nonproprietary names will facilitate pharmacovigilance when other means to track a specific dispensed product are not readily accessible or available; facilitate accurate identification of these biological products by health care practitioners and patients; and help prevent inadvertent substitution that may lead to medication errors. As the guidance explains, a distinguishing suffix supports the tracking of product-specific events over time, our ability to track adverse events to a specific manufacturer (and as appropriate, to a lot or manufacturing site for a particular biological product), and our ability to detect safety signals throughout the life cycle of a product so that the Agency and the manufacturer can act swiftly and in a targeted manner to identify and address a problem. As noted above, the drug substance proposed in this submission, ranibizumab, is essentially unchanged with respect to product quality attributes. Also, as noted above, Genentech is the license holder for BLA 125156 and the Applicant for BLA 761197.

Given the above factors, a suffix would not be designated in this particular case. The addition of a suffix to the nonproprietary name of the proposed formulation, while not adding the suffix to the marketed formulation of Lucentis, could create confusion and would not further the goals of the naming convention.

20.1 Package Insert and Instructions for Use

Listed below is the Package Insert and multiple Instructions for Use for the various procedures which involve the Port Delivery System (Initial Insertion, Refilling, Removal). During the review, multiple reviewers have provided comments and recommendations on the labeling. There were multiple conflicts in recommendations between reviewers. The Division of Ophthalmology has arbitrated between these conflicts and agrees with the final versions included below.

93 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

21. Post-marketing Requirements and Commitments

21.1 Post-marketing Requirement

The increased sustained level of ranibizumab in the aqueous raises a question about health of the corneal endothelial cells. The applicant will be required to conduct a controlled study in which the health of the corneal endothelial cells are evaluated by monitoring the number/density of corneal endothelial cells over a period of at least one year while receiving the 100 mg/mL ranibizumab administered through the Port Delivery System.

21.2 Post-marketing Commitment

The commitment is to perform real-time Susvimo drug product commercial container closure system leachable studies using appropriate test methods to identify and quantify volatile organic compounds (VOC), semi-VOC, and non-VOC, and elemental impurities at regular intervals through the end of shelf-life. The leachables results will be updated annually in the BLA Annual Report. The final results of this study and the toxicological risk evaluation for the levels of leachates detected in the drug product will be provided in the final study report to the BLA.

22. Financial Disclosure

Table 14. Covered Clinical Studies: [Archway and Ladder]

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 78 Archway, 48 Ladder		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 1		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 12		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: See table below Significant payments of other sorts: See tables below Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: See table below Sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements?	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided?	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): See table below		
Is an attachment provided with the reason?	Yes ☒	No ☐ (Request explanation from Applicant)

Reference ID: 4876724

Study GR40548

Last name	First Name	Clinical Site Number(s)	Role	No. Patients enrolled per site	Disclosure
(b) (6)			Subinvestigator	(b) (6)	Research grants for site >$200,000
			Subinvestigator		Consulting/speaker fees $4,000 Research grants for site >$50,000
			Subinvestigator & Investigator		Consulting/speaker fees <$50,000 Research grants for site >$200,000
			Investigator		Consulting/speaker fees $26,324
			Investigator		Consulting, Advisory Board, and Speaking $75,000
			Sub-investigator		Employment, Contracting, and Consulting $76,000
			Sub-investigator		Speaker fees $30,000
			Sub-investigator		Research, training, and consulting fees $152,000
			Investigator		Training, speaker fees $30,378.11

Study GR 40549

(b) (6)			Investigator	(b) (6)	Research grants for site >$200,000
			Investigator		Consulting/speaker fees $4,000 Research grants for site >$50,000
			Investigator		Consulting/speaker fees $26,324
			Investigator		Employment, Contracting, and Consulting $76,000
			Investigator		Contracting, consulting, and employment with Sponsor >$70,000
			Investigator		Research, training, and consulting fees $152,000

Study GX28228

(b) (6)			Sub-investigator	(b) (6)	Speaker's bureau >$25,000
			Sub-investigator		Consultant fees and advisory boards >$25,000
			Sub-investigator		Development partner stock >$50,000
			Investigator		Speaker honoraria >$25,000 Research contract >$50,000
			Sub-investigator		Research contract >$50,000
			Sub-investigator		Consultant fees and advisory boards >$25,000 Research contract >$50,000

23. Regulatory Action

The submitted BLA application as amended will be approved.

William M. Boyd, MD	Cross Discipline Team Leader
Wiley A. Chambers, MD	Division Director

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILEY A CHAMBERS
10/22/2021 10:06:41 AM

WILLIAM M BOYD
10/22/2021 10:29:44 AM