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APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

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Product:	Port Delivery System with Ranibizumab (PDS)
Indication:	Treatment of neovascular age-related macular degeneration (nAMD)
Applicant:	Genentech, Inc
Review Division:	Division of Ophthalmology
Reviewer:	María I Rivera, PhD, DPT-RPURM/SM
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Unless otherwise specified, all figures and tables are excerpted from the BLA.

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1 Executive Summary

1.1 Introduction

Genentech is seeking approval, in accordance with 21 CFR Part 601.2, of an original Biologics License Application for the use of Port Delivery System (PDS) with ranibizumab in the treatment of neovascular age-related macular degeneration (nAMD). Ranibizumab is a recombinant humanized IgG1κ isotype monoclonal antibody antigen-binding fragment (Fab) targeted against vascular endothelial growth factor A (VEGF-A). Ranibizumab has been FDA approved since 2006 as Lucentis® (BLA 125156, Genentech, Inc) for intravitreal (IVT) injection in the treatment of nAMD and other retinal vascular diseases.

The PDS with ranibizumab (PDS, also referred to as RPDS) is an innovative, intraocular drug delivery system that consists of an intraocular implant, a customized formulation of ranibizumab (100 mg/mL), and 4 ancillary devices used to fill, insert, refill-exchange and explant the implant (an initial fill needle, an insertion tool handle, a refill needle, and an explant tool, respectively). The RPDS implant is a refillable, permanent intraocular device uniquely designed for the continuous delivery of ranibizumab for at least 6 months.

The recommended dose of ranibizumab is 2 mg (0.02 mL of 100 mg/mL solution) continuously delivered via the permanent PDS implant with refills every 24 weeks (approximately every 6 months).

1.2 Brief Discussion of Nonclinical Findings

The pivotal nonclinical studies supporting this application included a 6-month ocular toxicity study in minipigs with 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 PDS 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 panophthalmitis. 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. Per summary information in the Toxicology Written Summary (Module 2.6.6, page 6 and 25), no safety signal relating to intraocular inflammation has been seen to date with the pivotal clinical RPDS data. 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 C_{max} 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 postdose, lower concentrations at 24 hours postdose, 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.

The adequacy of the biocompatibility testing data to support the ocular safety of the implant is under the purview of CDRH review team.

1.3 Recommendations

1.3.1 Approvability

Approval is recommended.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

(b) (4)

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

2 Drug Information

2.1 Drug

CAS Registry Number: 347396-82-1

Generic Name: Ranibizumab

Code Name: RO4893594, rhuFab V2

Chemical Name: Immunoglobulin G1, anti-human VEGF Fab fragment (human-mouse monoclonal rhuFab V2 G1-chain), disulfide with human-mouse monoclonal rhuFab V2 k-chain

Molecular Formula/Molecular Weight: The calculated molecular mass of intact ranibizumab is 48,379 Da (peptide chains only).

Structure or Biochemical Description: Ranibizumab is the antigen-binding fragment (Fab) of a humanized monoclonal antibody based on a human IgG1 framework containing heavy chain VHIII and light chain VLκI subgroup sequences. The recombinant antibody fragment is produced in E. coli and consists of one heavy chain (231 amino acid residues) and one light chain (214 amino acid residues).

Pharmacologic Class: Vascular endothelial growth factor (VEGF) inhibitor

Ranibizumab binds to all known biologically active forms of VEGF and neutralizes their activities. Ranibizumab binds specifically to a region of VEGF that is recognized by VEGF receptors on endothelial cells.

2.2 Relevant INDs, NDAs, BLAs and DMFs

- IND 113552 –Port Delivery System for Ranibizumab (Genentech, Inc)
- BLA 125156 – Lucentis® (Ranibizumab IVT injection) (Genentech, Inc.)

2.3 Drug Formulation

Ranibizumab for Port Delivery System (ranibizumab PDS) drug product is provided as a preservative-free, sterile, clear to slightly opalescent, colorless to slightly brownish solution for IVT use with the PDS.

Each single-use, 2 mL vial is designed to deliver a nominal 10 mg per 0.1 mL of ranibizumab, when administered as intended with the PDS. The drug product is formulated as 100 mg/mL ranibizumab (at target pH 5.5), with the composition shown in Table 1. The PDS implant is designed to contain approximately 20 µL (2 mg) of ranibizumab solution when filled.

Table 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) mM[b]	(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)			USP-NF/Ph. Eur./JP

a (b) (4)

b (b) (4)

The PDS with ranibizumab is a novel drug delivery system that consists of an intraocular implant; a customized formulation of ranibizumab for PDS (100 mg/mL); and four ancillary devices used to fill, insert, refill, and explant the implant (i.e., an initial fill needle [IFN], an insertion tool assembly [ITA], a refill needle [RFN], and an explant tool [ET], respectively), as summarized (Table 2).

Table 2: Device Constituents of the PDS

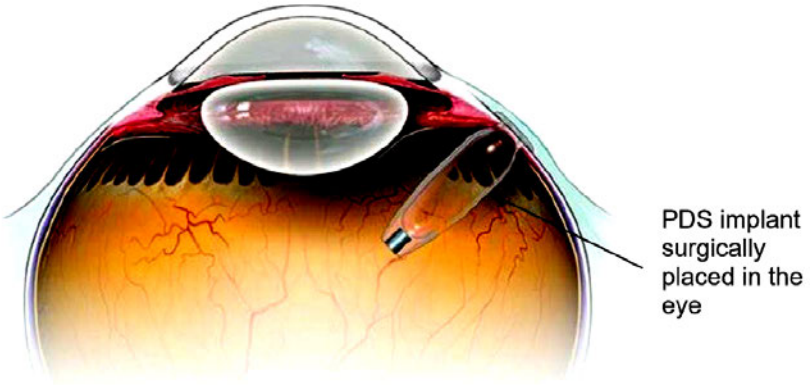
Device	Purpose
Implant	Provides continuous release of ranibizumab into the vitreous over time. The implant is intended to be permanent
Insertion Tool Assembly	Facilitates handling of the implant during initial filling and implant insertion procedures (consists of an insertion tool [IT] handle and IT carrier)
Initial Fill Needle	Fills the implant with ranibizumab PDS prior to insertion
Refill Needle	Refills (*in situ*) the implant with ranibizumab PDS when needed
Explant Tool	Grasps and securely holds the implant flange during explant procedure (if needed)

Figure 1 provides a schematic representation of the PDS device and Figure 2 provides an illustration of the PDS implant placed in the eye. The PDS implant is a refillable, permanent intraocular device uniquely designed for the continuous delivery of ranibizumab (100 mg/mL) for at least 6 months. Therefore, the PDS is designed to maintain therapeutic drug concentrations in the vitreous for longer durations than the available anti-VEGF treatments administered by IVT injection. The primary mode of action of the PDS is provided by ranibizumab.

Figure 1: Illustration of the Implant

The implant is surgically placed through the pars plana of the eye. The distal end of the implant extends into the vitreous humor with the proximal end accessible through the conjunctiva. When in place, an injection port is visible through the conjunctiva, and ranibizumab is refilled into the device through a septum that is in contact with the conjunctiva, and thus does not require repeated penetration of the sclera or choroid.

Figure 2: Illustration of the Implant after Surgical Placement in the Eye



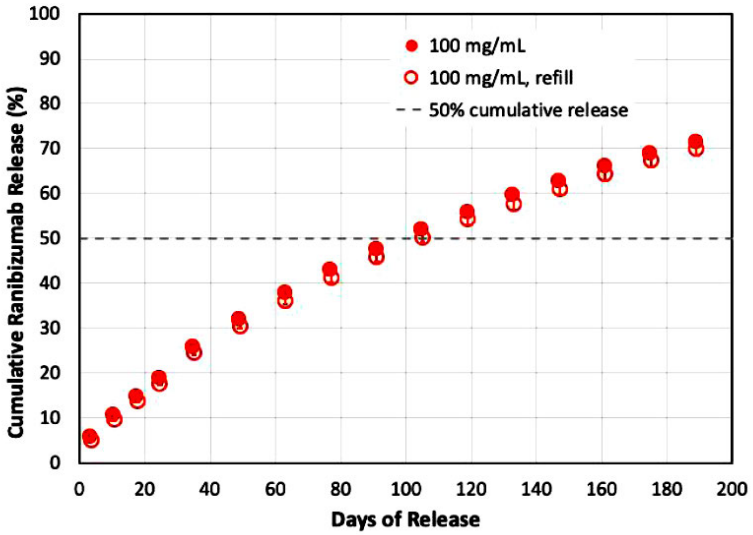
RPDS Drug Release Data:

Detailed release information is presented in Module 3.2R Regional Information (R.4.1 Implant) and Module 2.7.1 Biopharmaceutical Studies and Associated Analytical Methods. Some excerpts are shown below:

- The ranibizumab release from the PDS implant has been characterized in vitro using PBS buffer. The in vitro characterization supports that the PDS implant continuously releases therapeutic levels of ranibizumab for at least 24 weeks. Over the course of 24 weeks, the cumulative release is around 66%, i.e., 1.3 mg ranibizumab is released from the PDS implant when filled with 2 mg ranibizumab (20 µL of 100 mg/mL) (Figure 3).
- The half-life (when half of the original drug load is released) for a ranibizumab (100 mg/mL)-filled implant has been calculated to be 99 days.

Figure 3: Cumulative Ranibizumab Release for 100 mg/mL Implants with Initial Fill and Refill

Figure R.4.1-7 Cumulative Ranibizumab Release for 100 mg/mL Implants with Initial Fill and Refill



- Evaluation of both the total (Figure 4) and the active (amount of drug released with measurable VEGF binding activity) (Figure 5) ranibizumab release rates demonstrated consistent release profiles with the 100 mg/mL Phase II and Phase III formulations. The data support the commercial ranibizumab PDS formulation is identical to the Phase III formulation; therefore, no change in the drug release is expected.
    - Detailed information about release rate is provided in Section 6.1.8.4 (Module R.4.1 Implant).
    - The average daily release rate decreases exponentially over time. From Figure 4 below, it seems that the release rate is initially around 18 µg/day. The estimated release rate based on this in vitro characterization is 3.55 µg/day at 26 weeks.

- The total and active release rate curves for both the Phase II and Phase III formulations are very comparable as ranibizumab VEGF-binding activity is maintained above 85% through 28 weeks of in vitro drug release.

Figure 4: Total Drug Release Rates with Phase II and Phase III Formulations (In Vitro)

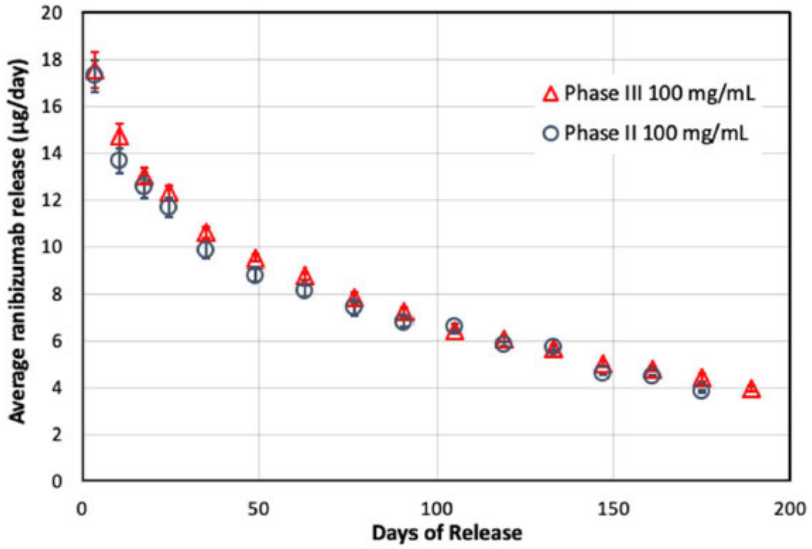


Figure 5: Active Drug Release Rates with Phase II and Phase III Formulations (In Vitro)

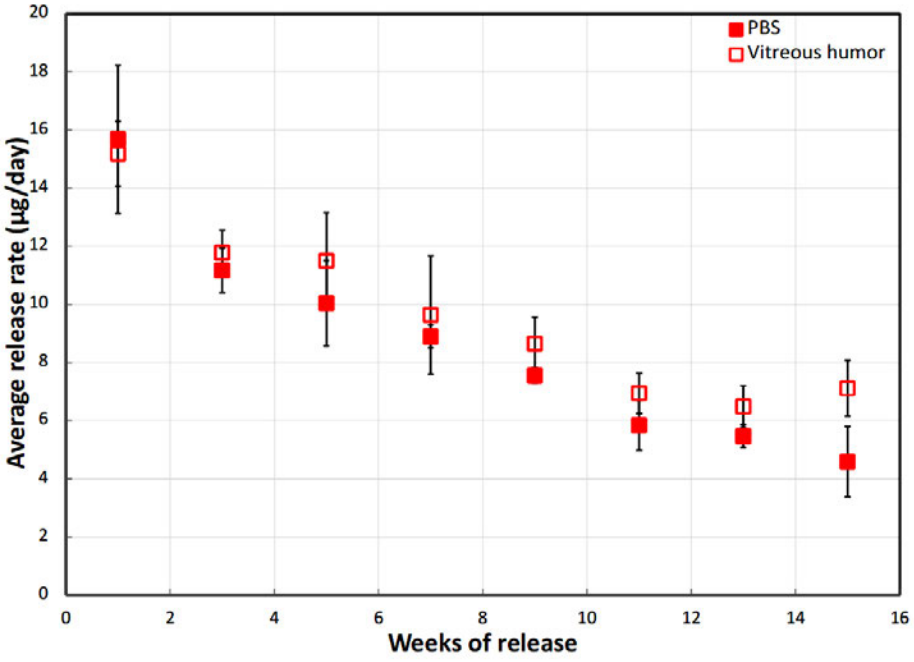
Reviewer's comments: *From these figures, it appears the steepest release occurs during the first 7 to 8 weeks. The cumulative release over the course of 24 weeks (around 66%; 1.3 mg ranibizumab) from the PDS implant when filled with 2 mg ranibizumab (20 µL of 100 mg/mL) is less than the total amount of ranibizumab administered with monthly dosing of Lucentis® during the same treatment duration (0.5 mg X 6 months = 3.0 mg) .*

From the cumulative release data, following an initial fill at the intended dose (2 mg; 0.02 mL of a 100 mg/mL), the total release over a period of 28 days was approximately 15% of the implant ranibizumab content (~0.3 mg over 28 days). This is 60% of the 0.5 mg approved monthly dose of Lucentis®.

The maximal drug released per day, approximately 18 µg/day, is 4% the approved 0.5 mg monthly dose of Lucentis®.

- In vitro release studies were also conducted in pooled cadaver human vitreous. The drug release rate was similar in both PBS and human vitreous (Figure 6).

Figure 6: Release Comparison of Ranibizumab When Using PBS and Vitreous Humor as Release Media



2.4 Comments on Novel Excipients

No novel excipient was used.

2.5 Comments on Impurities/Degradants of Concern

Pending CMC review

2.6 Proposed Clinical Population and Dosing Regimen

Patients with neovascular (wet) age-related macular degeneration (AMD).

- The recommended dose is 2 mg continuously delivered via the permanent implant with refills every 24 weeks (approximately 6 months)
- Supplemental treatment with 0.5 mg IVT ranibizumab injection may be administered in the affected eye if clinically necessary.

2.7 Regulatory Background

- Pre-IND 113552 briefing document submitted on 10-10-11; Nonclinical review by Conrad H. Chen, PhD, filed in DARRTS on 11-10-11; Sponsor meeting held on 11-3-11.
    - Main nonclinical recommendation was that an ocular toxicity study for Phase 2 RPDS be conducted for the BLA submission. The Applicant had used a scaled-down size implant in rabbits. A recommendation was given to conduct an ocular toxicity study with the full-sized RPDS used in the clinical trial and planned for marketing; use of a larger animal model was recommended.
- Initial IND 113552 submitted on 6-8-15 - Nonclinical review by Ilona Bebenek, PhD, filed in DARRTS on 7-6-15.
    - The recommendation (given during meeting on 11/3/11) to use the clinical product in an ocular toxicity study was not followed by the Applicant. Instead, a scaled down nonfunctional (no ranibizumab) implant was used in rabbits.
    - The nonclinical data alone was not sufficient to support the safety of this IND. The empty implant was determined to be tolerable in rabbits.
    - Decision to proceed was deferred to the CDRH team regarding safety of the RPDS device, and to the clinical team regarding safety of the proposed ranibizumab doses, based on previous clinical studies.
- End-of-Phase 2 briefing document submitted on 2-1-18; Sponsor meeting held on 3-23-18; Nonclinical review filed in DARRTS on 3-16-18.
    - Pharm/Tox agreed that based on the information provided, no additional nonclinical studies were required to support Phase 3 or BLA submission.
    - Cursory review of 6-month ocular toxicity study of the RPDS in minipigs (Study # 14-2350) was conducted by this reviewer.
- Pre-BLA briefing document submitted on 9-19-19; Sponsor meeting held on 11-6-19.
    - Pharm/Tox agreed with Applicant's proposal for content and format for nonclinical sections.

3 Studies Submitted

3.1 Studies Reviewed

- A 6-Month Ocular Toxicity Study with the Ranibizumab Port Delivery System (RPDS) in Female Yucatan Minipigs (Study # 14-2350)

- Previously reviewed under IND 113552
  - A 61-Day Mini-Swine PK Study Using Intravenous, Intravitreal, or Ocular Administration Via the Ranibizumab Port Delivery System (RPDS) (Study #13-2666)
  - A 2-Month Pilot Ocular Tolerability Study with a Nonfunctional Polysulfone (b) (4) Port Delivery System (Surrogate Kit 106-411-052) in Female New Zealand White Rabbits (Study #13-1963; non-GLP)
  - 6-Month Ocular Study with Scaled Nonfunctional Polysulfone (b) (4) Port Delivery System in Male and Female New Zealand White Rabbits (Study # 14-0137)

3.2 Studies Not Reviewed

- Studies under Module 4.2.2.1 Analytical Methods and Validation Reports
- Studies under Module 4.2.3.6. Local Tolerance – See CDRH review.
- 8-Day Ocular Surgery Study with Ranibizumab Port Delivery System (RPDS) in Male Yucatan Minipigs (Study # 16-0261)

3.3 Previous Reviews Referenced

- Pre-IND 113552 briefing document nonclinical review, Conrad H. Chen, PhD, filed in DARRTS on 11-10-2011
- IND 113552 SD # 10 (initial IND) nonclinical review, Ilona Bebenek, PhD, filed in DARRTS on 7-6-2015
- IND 113552 SD # 13 (6-month ocular tolerability study of the implant alone) nonclinical review, Ilona Bebenek, PhD, filed in DARRTS on 8-26-2015
- Nonclinical review, SD # 34, sBLA to support revision of US package insert; reference to review by Janice Lansita, PhD BLA 125156/s69 SD # 28 (review of developmental/reproductive toxicity), Lori Kotch, PhD, filed in DARRTS on 7-28-2012
- IND 113552 SD # 64 (End-of-Phase 2 briefing document) nonclinical review, María I Rivera, PhD, filed in DARRTS on 3-16-2018
- Nonclinical review BLA 125156 Lucentis® (Genentech), approved 6-30-2006, Zhou Chen, MD, PhD.

4 Pharmacology

4.1 Primary Pharmacology

No new studies were conducted. Ranibizumab administered via IVT injection was first approved for use in nAMD under the tradename Lucentis® (ranibizumab injection) by the FDA in June 2006, and by the European Medicines Agency (EMA) in January 2007. Subsequently, Lucentis® have been approved for other ocular vascular conditions

including macular edema following retinal vein occlusion, diabetic macular edema, diabetic retinopathy, and myopic choroidal neovascularization.

Ranibizumab is a recombinant humanized IgG1κ isotype monoclonal antibody (mAb) antigen-binding fragment (Fab) targeted against vascular endothelial growth factor A (VEGF-A). The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation.

(b) (4)

only binding to VEGF is included in the approved Lucentis® label. (b) (4) studies submitted for Lucentis BLA 125156 show binding data is comparable among all 3 isoforms (see tables excerpted from the nonclinical review of BLA 125156 below).

Study # BARD_4.FBV.0.RPT.3_0: Binding of Ranibizumab to Various Isoforms of VEGF by Surface Plasmon Resonance (Biacore Technology)

Apparent affinity of ranibizumab for three recombinant human VEGF isoforms

	$VEGF_{165}$	$VEGF_{121}$	$VEGF_{110}$
ka (M^{-1} sec^{-1})	(5.6± 0.28) x 10^4	(10.1± 2.3) x 10^4	5.2 ± 0.02) x 10^4
kd (sec^{-1})	≤ 10^{-5}	≤ 10^{-5}	≤ 10^{-5}
K_A (M^{-1})	≥ 5.6 x 10^9	≥ 10.1 x 10^9	≥ 5.2 x 10^9
K_D (pM)	≤ 179	≤ 99	≤ 192

M: molar

Study # 05-0852-1757: Analysis of Ranibizumab Binding to VEGF Isoforms (Biacore 3000 Surface Plasmon Resonance)

Apparent affinity of ranibizumab for three recombinant human VEGF isoforms (mean ± SD)

	$VEGF_{165}$	$VEGF_{121}$	$VEGF_{110}$
ka (x 10^4 M^{-1} sec^{-1})	3.85±0.10	4.04± 0.15	7.37± 0.61
kd (sec^{-1})	< 10^{-5}	< 10^{-5}	< 10^{-5}
K_D (pM)	<260	<248	<136

M: molar

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

A PK study was conducted in minipigs. The study was previously reviewed (IND 113552 SD # 10 nonclinical review, Ilona Bebenek, PhD, filed in DARRTS on 7-6-2015). Key findings, per Dr Bebenek review are listed below. Additional comments by this reviewer are shown in *italics*.

A 61-Day Mini-Swine PK Study Using Intravenous, Intravitreal, or Ocular Administration Via the Ranibizumab Port Delivery System (RPDS) (Study #13-2666)

The study design was the following:

Group Designations and Dose Levels

Group	Number of Female Animals	Dose Route	Target Dose Level	Target Dose Volume	Samples Collected
1[a]	9	IVT (OU)	0.5 mg/eye	50 µL/eye	Blood and ocular tissues
2[b]	3	IV	0.5 mg/animal	1.25 mL/animal	Blood
3[c]	14	RPDS (OD)	2.3 mg	23 µL preloaded in RPDS	Blood and ocular tissues
NA	2[d]	NA	NA	NA	Control ocular tissues[d]

IV Intravenous.
IVT Intravitreal.
NA Not applicable.
OD Right eye.
OU Both eyes.
RPDS Ranibizumab Port Delivery System.
a Each animal received a single intravitreal dose in each eye.
b Each animal received a single bolus intravenous injection.
c Each animal received a surgically implanted RPDS and a dose of Lucentis® (100 mg/mL) via the RPDS on Study Day 1 and a second dose of Lucentis® (100 mg/mL) via the RPDS on Study Day 46 in the right eye only.
d These animals received no treatment and had only control ocular tissues collected (Protocol Deviation).

Following a single bilateral IVT administration of Lucentis (0.5 mg/eye) to each eye for animals in Group 1, samples of serum, aqueous humor, vitreous humor, and retina were collected on Days 5, 12, and 18. Following a single intravenous administration of Lucentis to animals in Group 2 (0.5 mg/animals), only samples of serum were collected at 0.5, 1, 2, 4, 8, 24 (Day 2), 48 (Day 3), and 72 (Day 4) hours postdose. Following a unilateral IVT administration of Lucentis (2.3 mg) via RPDS to the right eye of animals in Group 3 on Days 1 and 46, samples of serum were collected at specific time points through Study Day 61, and aqueous humor, vitreous humor, retina, and RPDS were collected on Study Day 61.

Key findings:

- In animals treated with a single IVT injection of ranibizumab, vitreous humor concentrations of Lucentis® were observed at a maximum on Day 5 (the first vitreous time point sampled). On Study Day 12, the concentrations had declined, but were still quantifiable on Study Day 18 *(last timepoint sampled)*.
- Vitreous humor concentrations in the implanted animals were determined on Study Day 61, approximately 2 weeks following the RPDS refill of Lucentis® on Study Day 46. Lucentis® was quantifiable in all right eyes on Day 61, but Lucentis® was not observed in the contralateral undosed (left) eye.

- *Comparison of the Lucentis concentrations in the vitreous after ITV (Group 1) injection or after RPDS implantation (Group 3) are shown in Table 3.*

Table 3: Lucentis Concentrations in the Vitreous of Animals Treated with an Intravitreal Injection (Group 1) or the RPDS Implant Group 3)

Group ID	Animal ID	Eyes	Time Point (day)	Assay Result (µg/mL)	Matrix
1	MM130134	OD	Control	LTR	Vitreous Humor
1	MM130134	OS	Control	LTR	Vitreous Humor
1	MM130143	OD	Control	LTR	Vitreous Humor
1	MM130143	OS	Control	LTR	Vitreous Humor
1	M03087	OD	5	113.2	Vitreous Humor
1	M03087	OS	5	97.8	Vitreous Humor
1	M03090	OD	5	126.3	Vitreous Humor
1	M03090	OS	5	99.1	Vitreous Humor
1	M03093	OD	5	38.1	Vitreous Humor
1	M03093	OS	5	130.2	Vitreous Humor
1	M03088	OD	12	50.0	Vitreous Humor
1	M03088	OS	12	53.5	Vitreous Humor
1	M03091	OD	12	8.4	Vitreous Humor
1	M03091	OS	12	54.2	Vitreous Humor
1	M03094	OD	12	63.8	Vitreous Humor
1	M03094	OS	12	56.9	Vitreous Humor
1	M03089	OD	18	25.2	Vitreous Humor
1	M03089	OS	18	26.9	Vitreous Humor
1	M03092	OD	18	27.8	Vitreous Humor
1	M03092	OS	18	32.2	Vitreous Humor
1	M03095	OD	18	23.5	Vitreous Humor
1	M03095	OS	18	25.4	Vitreous Humor
3	M03099	OD	61	55.7	Vitreous Humor
3	M03099	OS	61	LTR*	Vitreous Humor
3	M03100	OD	61	53.4	Vitreous Humor
3	M03100	OS	61	LTR	Vitreous Humor
3	M03101	OD	61	65.1	Vitreous Humor
3	M03101	OS	61	LTR	Vitreous Humor
3	M03102	OD	61	42.4	Vitreous Humor
3	M03102	OS	61	LTR	Vitreous Humor
3	M03103	OD	61	136.2	Vitreous Humor
3	M03103	OS	61	LTR	Vitreous Humor
3	M03104	OD	61	49.6	Vitreous Humor
3	M03104	OS	61	LTR	Vitreous Humor
3	M03105	OD	61	72.8	Vitreous Humor
3	M03105	OS	61	LTR	Vitreous Humor
3	M03106	OD	61	62.8	Vitreous Humor
3	M03106	OS	61	LTR	Vitreous Humor
3	M03107	OD	61	33.9	Vitreous Humor
3	M03107	OS	61	LTR	Vitreous Humor
3	M03108	OD	61	260.8	Vitreous Humor
3	M03108	OS	61	LTR	Vitreous Humor
3	M03109	OD	61	55.3	Vitreous Humor
3	M03109	OS	61	LTR	Vitreous Humor
3	M03110	OD	61	23.9	Vitreous Humor
3	M03110	OS	61	LTR	Vitreous Humor
3	M03111	OD	61	58.3	Vitreous Humor
3	M03111	OS	61	LTR	Vitreous Humor
3	M03112	OD	61	35.0	Vitreous Humor
3	M03112	OS	61	LTR	Vitreous Humor

LTR Lower than reportable.
OD Right eye.
OS Left eye.

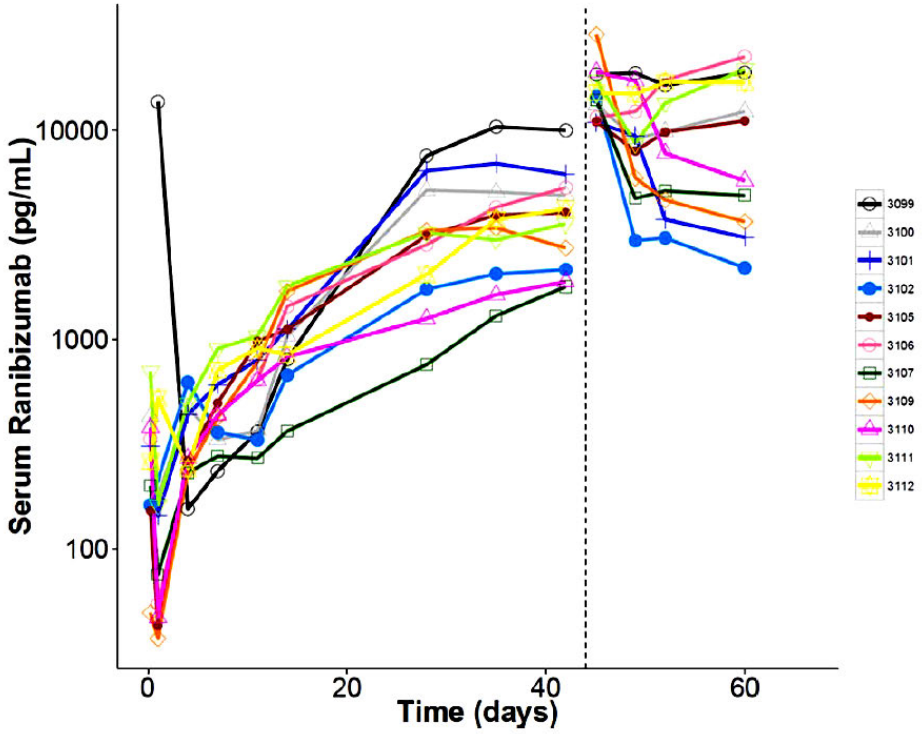
- *Lucentis vitreous humor concentrations after IVT injection at the clinical dose of 0.5 mg/eye (Group 1) ranged from 38 to 130 µg/mL on Day 5 (1st timepoint evaluated) and decreased to 23 to 32 µg/mL on Day 18. In animals receiving the RPDS (Group 3), Lucentis vitreous humor concentrations ranged from 23.9 to 136.2 µg/mL on Day 61 (excluding*

animal # M03108 with much higher concentrations considered related to inadvertent injection of the refill dose into the vitreous), approximately 2 weeks following the RPDS refill.

- *Although the study design does not allow for a full side-to-side comparison of vitreous levels between IVT injection and RPDS implant because of limited PK sampling in RPDS-treated animals, ranibizumab concentrations in the vitreous were in general comparable to those observed after IVT injection at a similar timepoint (i.e., Days 12 and 18 postdose).*

- Following a single intravenous administration of Lucentis®, the maximal serum concentrations *(418000 to 419000 pg/mL)* were observed at the first sampling time point (0.5 hours postdose). *The serum concentrations declined to levels ≤1190 pg/mL by 24 hours postdose, but were near or below the lower limit of quantitation at 48 and/or 72 hours postdose*.
- Following a single IVT injection to both eyes in Group 1 animals, serum concentrations of Lucentis® reached a maximum for most animals at 6 hours (1st timepoint evaluated) or 24 hours postdose (5070 to 17100 pg/mL). After reaching the maximum concentration, serum levels of Lucentis® declined over the remaining study period but were still quantifiable on Day 18 (888 to 3670 pg/mL).
- Following administration of Lucentis® via RPDS, the serum concentrations appeared to exhibit a biphasic pattern (Figure 7). Generally, the animals in this group had high concentrations at 6 hours postdose, lower concentrations at 24 hours postdose, and then the serum concentrations were observed to rise over the next couple of weeks.
    - *After the first dose, the serum levels of Lucentis® appeared to reach a plateau over Days 36 to 43, with concentration ranging from 1640 to 10400 pg/mL (values excludes the 3 animals considered as outliers, see Figure 7).*

Figure 7: Individual Serum Concentrations following RPDS Initial Release and Refill (Removed Outliers) in Minipigs



RPDS=ranibizumab port delivery system.

Note: Data from 3 animals was excluded: Animal # M03103 (damage to the needle during refill; Animal # M03104 (device not easy to see during refill); Animal # M03108 (damage to the needle during refill; inadvertently injected into the vitreous)

- *The serum levels achieved after the first dose via the RPDS were overall lower than those achieved after IVT administration of 0.5 mg Lucentis at similar timepoints through Day 15.*
- *Concentrations of Lucentis® in serum generally increased following the refill of the RPDS on Study Day 46. After the second refill, Lucentis concentrations on Day 61 (2 weeks after the refill dose on Day 46) ranged from 2200 to 22500 pg/mL (still comparable to the maximal range observed with IVT Lucentis®).*

- Individual and mean serum PK parameters in RPDS Group 3 are shown in the table below.

Table 4: RPDS Group 3 Individual and Summary Statistics of Ranibizumab Pharmacokinetic Parameters in Serum

RPDS	Before RPDS Refill				After RPDS Refill			
Animal No.	C_{max} (ng/mL)	C_{trough_42d} (ng/mL)	AUC_{0-42} (ng/mL • day)	$t_{1/2}$ (day)	C_{max} (ng/mL)	C_{trough_60d} (ng/mL)	AUC_{45-60} (ng/mL • day)	$t_{1/2}$ (day)
M03099	35.0	10.0	227	NA	18.9	18.9	269	NA
M03100	13.2	4.89	120	NA	13.2	12.3	161	NA
M03101	10.9	6.17	154	NA	10.9	3.08	86.3	8.08
M03102	14.5	2.16	50.8	NA	14.5	2.20	59.0	23.0
M03103	27.6	3.47	75.5	NA	NA	NA	NA	NA
M03104	10.3	1.70	56.4	NA	NA	NA	NA	NA
M03105	11.0	4.04	90.3	NA	11.1	11.1	148	NA
M03106	11.5	5.33	95.5	NA	22.5	22.5	252	NA
M03107	14.0	1.79	29.3	NA	14.0	4.88	89.0	NA
M03108	13.4	3.79	88.2	NA	NA	NA	NA	NA
M03109	28.7	2.74	87.8	NA	28.7	3.66	107	17.0
M03110	19.0	1.89	43.2	NA	19.0	5.74	162	7.96
M03111	17.4	3.58	91.8	NA	19.6	19.6	216	NA
M03112	15.1	4.21	77.2	NA	17.0	16.9	243	NA
n	14	14	14	NA	11	11	11	4
Mean	17.3	3.98	91.9	NA	17.2	11.0	163	14.0
SD	7.70	2.21	50.0	NA	5.32	7.51	73.4	7.32
%CV	44.6	55.5	54.5	NA	30.9	68.4	45.1	52.3
Min	10.3	1.70	29.3	NA	10.9	2.20	59.0	7.96
Median	14.3	3.69	88.0	NA	17.0	11.1	161	12.5
Max	35.0	10.0	227	NA	28.7	22.5	269	23.0

AUC_{0-42} = area under the serum concentration versus time curve from time = 0 to Day 42;
ACU_{45-60} = area under the serum concentration versus time curve from Day 45–60;
C_{max} = maximum observed concentration; $C_{trough\ 42d}$ = observed trough concentration at Day 42;
$C_{trough\ 60d}$ = observed trough concentration at Day 60; %CV = coefficient of variation;
min = minimum; max = maximum; RPDS = ranibizumab port delivery system; SD = standard deviation; $t_{1/2}$ = terminal half-life;

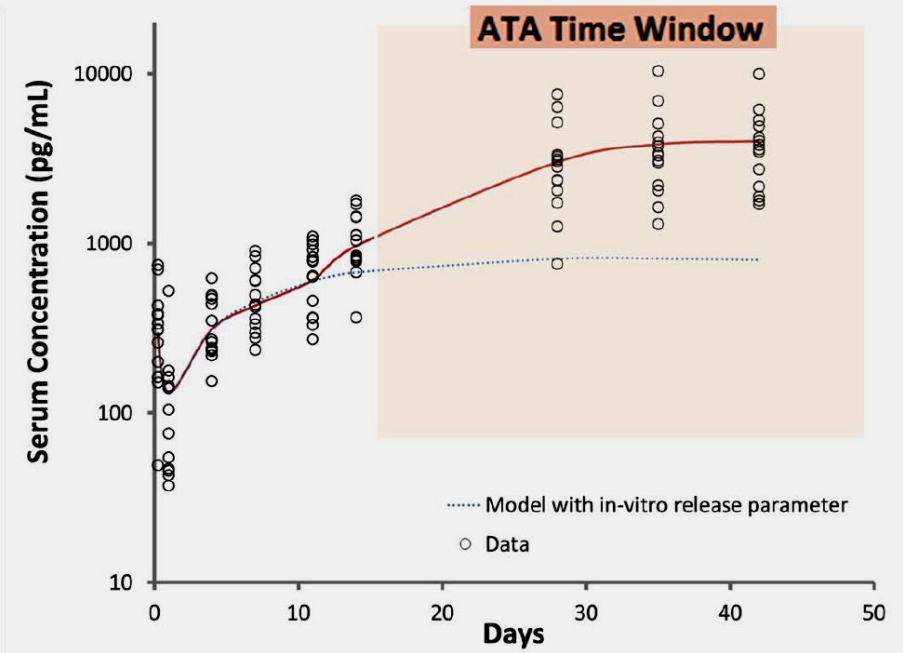
- *Although exposure was higher at most timepoints (reflected in the AUC values) after the refill dose, the C_{max} was generally consistent after administration of the initial and refill dose.*

- Following IVT injection of Lucentis® via RPDS to animals in Group 3, five animals had positive ATA results on Day 15, and all animals in the group tested positive for ATA on Study Days 29 and 61 (Table 3). Positive ATA results observed on Day 15 coincided with the time frame of an immune response to Lucentis®.
- The Applicant's hypothesis is that the cause of the increase in ranibizumab serum exposure (biphasic pattern) may be attributable to ATAs acting as carrier proteins for ranibizumab, thus decreasing ranibizumab clearance due to the addition of an Fc portion when ATA are complexed with the drug.

- *In contrast, in the 6-month ocular toxicity study in minipigs (Study # 14-2350 below), the ATA response led to decreased serum concentrations with each refill dose, achieving levels below the lower limit of quantitation for all except one animal after the final monthly refill (refill # 7).*
- *Therefore, the impact of ATA in the minipig was variable among the PK and TK studies (correlating with prolonged serum exposure in the PK study, and ultimately with decreased serum exposure in the TK study).*
- *The Applicant noted: "ATA have been observed to prolong systemic exposure to ranibizumab in the context of chronic exposure via intravitreal administration in cynomolgus monkey (Study # 08-0590). The variable impact of ATA across the studies described herein may have been caused by the presence of both clearing ATA and sustaining ATA; clearing ATA have been noted to increase systemic clearance via reticuloendothelial system-mediated recognition and removal of the ATA-drug complex, whereas sustaining ATA have been noted to decrease systemic clearance via FcRn-mediated recirculation of the ATA-drug complex (Ponce et al. 2009)."*

- Model prediction data was consistent with the empirical values prior to the development of an immune response (Figure 8).

Figure 8: Observed Serum Concentrations and Model Prediction following RPDS Initial Implantation



ATA = anti-therapeutic antibody; RPDS = ranibizumab port delivery system.
Note: Red line indicates median of data.

5.2 Toxicokinetics

See Study # 14-2350 below.

6 General Toxicology

6.1 Single-Dose Toxicity

Study # 14-2350 (see review under Section 6.2), a GLP 6-month toxicity study in minipigs, evaluated a cohort with a single dose of ranibizumab (2.3 mg) administered via the PDS (implant insertion followed for 6 months with no refill) in addition to a group with PDS implant insertion followed by monthly ranibizumab refills for a total of 7 doses (2.3 mg/refill).

6.2 Repeat-Dose Toxicity

Study title: A 6-Month Ocular Toxicity Study with the Ranibizumab Port Delivery System (RPDS) in Female Yucatan Minipigs

Study no.:	14-2350
Study report location:	EDR Module 4.2.3.2 \\CDSESUB1\evsprod\bla761197\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\14-2350.pdf
Conducting laboratory and location:	(b) (4) [redacted]
Date of study initiation:	Dec 23, 2014
GLP compliance:	Yes, with exceptions
	Exceptions included the equipment or software for data collection for ERG, OCT, digital imaging, and ophthalmic evaluations were not validated, not described in an SOP and/or lack documentation of instrument routine maintenance or calibration. It was stated in the Study Report that because no indication was noted of a malfunction that would have affected the collection of images, the images obtained with these instruments were of sufficient quality to allow image evaluation, and/or examinations were completed successfully, the particular equipment for each one of these evaluations performed appropriately.

	Based on identification of adverse findings, which correlated among the different types of ocular evaluations employed, this reviewer agrees that the exceptions did not appear to have a significant impact in the interpretation of the data or study validity.
QA statement:	Yes
Drug, lot #, and % purity:	Ranibizumab, lot # 507391, 98% pure • Ranibizumab Port Delivery System (RPDS) implants (Manufacturer: Phillips Medisize Corporation), lot # 33913058

Key Study Findings

- Sham surgery procedure was associated with minor ophthalmic abnormalities, while insertion of the implant was associated with more significant findings.
- The surgical procedure itself (e.g., sham surgery or the insertion of a RPDS implant) was associated with varying degrees of conjunctival hyperemia, chemosis, subconjunctival hemorrhage. These findings resolved by Day 8 or 29.
- The implant was associated with varying amounts of blood on the surface of the implant, red vitreal floaters (vitreous hemorrhage), white vitreous floaters, and yellow reddish material which appeared to be fibrin and blood throughout the vitreous, yellow-white exudate around the implant, vitreous haze, and implant protrusion/extrusion above the sclera.
    - The implant movement was considered due to anatomical differences between porcine and human eye[1]. However, implant dislocation was also observed in the clinical trials.
    - These ophthalmic findings decreased by Day 29 and resolved without consequence by Day 71 in most eyes.
- Administration of a single dose (2.3 mg, no refill) or multiple doses (monthly refills of 2.3 mg) of ranibizumab via RPDS was associated with increased severity of ocular inflammation, which necessitated unscheduled euthanasia for one animal after administration of the 5th monthly dose.
- The inflammation correlated with optical coherence tomography, fundus photography, and fluorescein angiogram findings of perivascular sheathing, epiretinal membrane formation, venous dilation, vascular leakage, capillary microaneurysms, optic nerve swelling, and increased hyper-reflective spots in the vitreous. Vitreous optic nerve traction or retinal detachment was observed only in eyes receiving multiple doses of ranibizumab administered via the implant.
- The findings supporting that the inflammation was related to an immunogenic reaction to ranibizumab (a humanized protein) include infiltrates of

[1] Bantseev V, Schuetz C, Booler HS, et al. Evaluation of surgical factors affecting vitreous hemorrhage following Port Delivery System with ranibizumab implant insertion in a minipig model. *Retina* 2020, **40(8)**:1520-1528.

lymphocytes/macrophages and plasma cells, perivascular sheathing, and systemic ATA presence.

- Administration of multiple doses of ranibizumab via RPDS was associated with an increased severity of peri-RPDS implant fibrosis and peri-RPDS implant inflammatory cells presence compared to administration of a single dose.
- No systemic toxicities were observed.
- Systemic ATA were detected in the serum of all (10/10) ranibizumab-treated animals and in none (0/5) of the animals in the control group. The presence of systemic ATA resulted in reduced serum concentrations of ranibizumab in most animals.
- Based on the ocular inflammation, there was no ocular NOAEL in the study.

Methods

Doses:	Nominal: 0 and 2.3 mg/eye/dose (see Study Design table below) Actual: 0 and 2.1 mg/eye/dose **Notes:** • Dose levels in the table below were based on a nominal dose volume of 23 µL/dose. The actual dose volume was 20.87 µL. • Right eye received the vehicle or test article-filled implant; left eye underwent sham surgery.
Frequency of dosing:	Monthly (total of 7 doses): Refills with the appropriate formulation were administered on Study Days 29, 57, 85, 113, 141, and 169, as shown in the table below. Group 2 received a single dose, i.e., the implant was not refilled.
Route of administration:	Surgical implantation through the sclera (at pars plana) into the vitreous cavity. One RPDS device containing the appropriate drug formulation was inserted into the right eye of each animal, and a sham surgery was conducted on the left eye.
Dose volume:	20.87 µL/dose
Formulation/Vehicle:	Ranibizumab vehicle
Species/Strain:	Yucatan Minipigs
Number/Sex/Group:	3-7 females/group, see Study Design Table below
Age:	3 to 4 months old
Weight:	10.0 to 12.3 kg

Satellite groups: None
Unique study design: None
Deviation from study protocol: None with an impact in the validity of the study

Study Design

Group	No. of Animals Female	Surgery Regimen[a] Right Eye	Surgery Regimen[a] Left Eye	Dosing Day(s)[a]	Dosing Regimen[b] Right Eye	Dosing Regimen[b] Left Eye	Right Eye Dose Level (mg/eye/dose)	Right Eye Dose Concentration (mg/mL)
1[c]	5	Implant	Sham	1, 29, 57, 85, 113, 141, 169	Vehicle (in RPDS)	Not dosed	0	0
2[d]	3	Implant	Sham	1	Test Article (in RPDS)	Not dosed	2.3	100
3[e]	7	Implant	Sham	1, 29, 57, 85, 113, 141, 169	Test Article (in RPDS)	Not dosed	2.3	100

RPDS = Ranibizumab Port Delivery System

a On Study Day 1, animals underwent surgery once and were implanted with the RPDS implant initially filled with their respective materials in the right eye, and a sham surgery in the left eye. Surgery for one replacement animal (Animal No. M03402, Group 3) occurred on Study Day 8.

b On Study Days 29, 57, 85, 113, 141, and 169, the implant for each animal in Groups 1 and 3 were refilled with respective materials for a total of 7 doses.

b Dose levels were based on a nominal dose volume of 23 µL/dose. The actual dose volume was 20.87 µL/dose.

c Control with refill

d No refill

e Refill

Observations and Results

Mortality (2X/day)

One Group 3 animal (# M03410) was euthanized early on Day 118 (5 days after administration of the 5th dose) due to severe mixed-cell panophthalmitis in the right eye. The severe inflammation correlated with clinical observations of conjunctival redness and eye squinting. Ophthalmic examinations showed 3+ conjunctival hyperemia, 3+ mucopurulent ocular discharge, 3+ diffuse corneal edema, 4+ aqueous flare, an inability to score aqueous/vitreous cell due to the anterior segment abnormalities, corneal neovascularization in 1 to 2 mm into the clear cornea (ciliary flush), 4+ vitreous haze, and a severely degraded view of the fundus. Slight to marked infiltrates of plasma cells, neutrophils, lymphocytes, and macrophages with concomitant moderate retinal detachment and photoreceptor nuclei drop-down were observed microscopically. This severe inflammation was considered related to an immune-mediated response to ranibizumab. This animal showed the highest ATA titers.

Clinical Signs (General: 2X/day; cageside: 1X/day; detailed: weekly)

PDS implantation (with or without ranibizumab) in right eyes was associated with greater incidence of red conjunctiva compared to left eyes of animals with sham surgery (Table 5).

Administration of multiple doses of ranibizumab via RPDS (Group 3) was associated with increased incidence of conjunctival redness. This finding correlated with ophthalmic findings of conjunctival hyperemia. Table 5 does not show the number of days the finding was observed per animal, which was clearly higher in multiple dose (Group 3) animals. In control (Group 1) and single dose (Group 2) groups, the finding was generally observed during the first month post implantation/dose administration. In animals treated with multiple ranibizumab doses via the RPDS (Group 3), the finding was observed beyond the first month and up to Day 131 to 143 (i.e., post 5th and 6th dose).

Table 5: Summary of Clinical Signs

Dose Level	1 Control	2 No Refill	3 Refill
Right Eye (mg/dose)	0 in RPDS	2.3 in RPDS	2.3 in RPDS
Left Eye (mg/dose)	0 (Sham surgery)	0 (Sham surgery)	0 (Sham surgery)
Phase: Dosing			
Category / Observation	Group/Sex: 1/F	2/F	3/F
	Number in Group: 5	3	7
Eyes			
conjunctiva, palpebral, eyes, red	5	3	7
conjunctiva, palpebral, left eye, red	2	1	0
conjunctiva, palpebral, right eye, red	4	2	7
dilated pupil, right eye	0	0	1
discharge, eyes, clear	1	0	2
discharge, eyes, red	0	0	2
discharge, left eye, clear	0	0	1
discharge, right eye, clear	1	0	1
discharge, right eye, white	0	0	1
squinting, right eye	0	0	1
swollen conjunctiva, right eye	0	0	1

Swollen conjunctiva noted in one Group 3 animal (# M03407) was related to the dissolvable suture adhering to the conjunctiva and therefore was considered procedure related. This observation did not correlate with ophthalmic findings.

Body Weights (Prior to dosing on Day 1, weekly during the dosing phase)

No test article-related effects

Feed Consumption (2X/day; qualitatively)

No test article-related effects

Ophthalmoscopy (Slit lamp and indirect ophthalmoscopy; predose and Days 1 (after surgery), 3, 6, 8, 15, 29, 57, 85, 113, 141, 169, and 176; animals in Groups 1 and 3 on Days 43, 71, 99, 127, and 155; on Days 29, 57, 85, 113, 141, and 169 in animals in Groups 1 and 3 prior to the refill procedure)

- Procedure-related findings:
  - Between Days 1 and 13, slit-lamp biomicroscopic findings were comparable between right and left eyes in all 3 groups indicating that there were no findings during this interval that were specifically attributable to the RPDS implant or ranibizumab via RPDS.
  - The surgical procedure itself (i.e., sham surgery or the insertion of a RPDS implant) was associated with varying degrees of conjunctival hyperemia, chemosis, and subconjunctival hemorrhage. During the period immediately following surgery, the conjunctival hyperemia and chemosis were often more prominent at the surgery site, or were entirely confined to the surgery site, and most likely were attributable to normal wound healing process and the presence of a dissolvable conjunctival suture in this location. Subconjunctival hemorrhage resolved without consequence by Day 8 in all eyes of all 3 groups.
  - Procedure-related vitreal hemorrhage (vitreous cell scores of 4+ red vitreous cell) was noted on slit lamp biomicroscopy on Day 6 in one right eye and on Day 8 in three right eyes from animals in Group 3. However, upon indirect ophthalmoscopy, the proportion of right eyes with blood on the surface of the implant or in the vitreous were comparable between all 3 groups indicating that blood within the vitreous was procedure-related rather than ranibizumab related through Day 13. The lack of a similar finding in sham-operated eyes suggest the blood in the vitreous was related to the implant insertion.
  - In the left eye (sham surgery), conjunctival hyperemia and chemosis were not observed after Day 29, which was a time corresponding to dissolution of the conjunctival suture. Ophthalmic examinations in sham-surgery eyes were normal after Day 29. Thus, any observations in RPDS-implanted and/or test article-dosed eyes noted after Day 29 were not considered related to the surgical procedure.

- Implant-associated findings:
  - Varying degrees of implant protrusion/extrusion above the sclera were sporadically observed in a few animals (starting on Day 155 in one control animal, on Days 85 and 113 in two animals administered a single dose of ranibizumab via RDPS, and on Days 43 and 71 in two animals administered multiple doses of ranibizumab via RDPS).
    - Per Study Report, the implants may not have been completely stable in pigs because they were designed for human sclera. However, implant dislocation was observed in the clinical trials.
  - In vehicle-filled implant control eyes (refilled monthly), procedure and implant-associated ophthalmic findings included prolonged, mild (and often

localized) conjunctival hyperemia over the implant, vitreous haze, blood on implant surface, red vitreous floaters (vitreous hemorrhage), and white vitreous floaters. These findings decreased by Day 29/Day43 and resolved by Day 71 (except for focal hyperemia 1+ noted at surgery site in one animal on Day 176). Findings attributed to the implant are shown in Table 6.

Table 6: Ophthalmic Examination Findings in Group 1 (Vehicle-Filled Implants - Right Control Eyes)

Finding	Study Day 15	Study Day 29	Study Day 43	Study Day 57	Study Day 71	Study Day 85	Study Day 99	Study Day 113	Study Day 127	Study Day 141	Study Day 155	Study Day 169	Study Day 176
Vitreous Cell													
Trace	-	-	-	-	-	-	-	-	-	-	-	-	-
1+	-	-	-	-	-	-	-	-	-	-	-	-	-
2+	-	-	-	-	-	-	-	-	-	-	-	-	-
3+	-	-	-	1	-	-	-	-	-	-	-	-	-
4+	1*	1	1	-	-	-	-	-	-	-	-	-	-
Vitreous Haze													
0.5	-	-	-	-	-	-	-	-	-	-	-	-	-
1	-	-	1	-	-	-	-	-	-	-	-	-	-
2	-	1	-	-	-	-	-	-	-		-		-
3	-	-	-	-	-	-	-	-	-	-	-	-	-
4	1	-	-	-	-	-	-	-	-	-	-	-	-
Blood on Implant	1	-	-	-	-	-	-	-	-	-	-	-	-
Fibrin or Exudate in Vitreous	1	-	1	-	-	-	-	-	-	-	-	-	-
White Vitreous Floaters	1	1	-	-	-	-	-	-	-	-	-	-	-

- = Finding not present at this interval; * = cells were red in color.

- **Ranibizumab via RDPS-Related Findings**
  - In eyes (right) treated with RPDS implant (Groups 1 and 3), implant/test article-related findings were noted beginning on Day 15 (Tables 7 and 8).
  - Single or multiple administration of ranibizumab via RPDS was associated with increased duration of vitreous cells (predominantly white) and vitreous haze and presence of yellow-red material in the vitreous for a longer period than in right eyes of animals administered the vehicle-filled implant control (Group 1). The opacification of the vitreous was enough to preclude evaluation of the details of the fundus in some eyes.
    - Per Study Report, vitreous haze was considered evidence of posterior segment inflammation in the absence of vitreous hemorrhage.

- The inflammation was more severe in animals administered multiple doses of ranibizumab via RPDS (Group 3) and typically greatest in the region immediately surrounding the implant.
- Incipient cataracts considered secondary to contact between the intraocular portion of the implant and the peripheral lens were noted in 2 Group 3 animals (animal # M03410 [euthanized early] on Day 113 and animal # M03406 from Day 99 onward).
- Subtle perivascular sheathing around retinal blood vessels was noted in one Group 3 animal (# M03405) on Day 127.
- These findings correlated with signs of inflammation (perivascular sheathing, vascular leakage, and/or capillary micro aneurysms) on fundus photography, FA, and OCT (see below).

Table 7: Ophthalmic Examination Findings in Right Eyes Administered a Single Dose of Ranibizumab via RPDS

Finding	Study Day 15	Study Day 29	Study Day 57	Study Day 85	Study Day 113	Study Day 141	Study Day 169	Study Day 176
Aqueous Flare								
Trace	-	-	-	1	-	-	-	-
Aqueous Cell								
Trace	-	-	-	-	1	-	-	-
1+	-	-	-	1	-	-	-	-
Incomplete pupil dilation	-	-	-	-	1	-	-	-
Vitreous Cell								
Trace	-	-	-	-	-	-	1	-
1+	1*	-	2	1	1	1	1	2
2+	-	-	-	1	1	1	-	1
3+	-	-	-	-	-	-	1	-
4+	-	1	1	1	1	1^	-	-
Vitreous Haze								
0.5	-	-	1	1	-	2	2	1
1	-	-	-	2	3	1	-	1
2	-	-	-	-	-	-	-	-
3	-	-	-	-	-	-	-	--
4	1	1	-	-	-	-	-	-
Fibrin/blood on Implant	1	1	-	-	-	-	-	-
Fibrin/Blood in Vitreous	1	-	-	-	-	-	-	-
Yellow-white Exudate in Vitreous or on Implant	-	1	1	1	1	-	-	-
Patchy areas of RPE Mottling	-	-	-	-	-	-	1	1

- = Finding not present at this interval; * = cells are red in color; ^ = cells are especially concentrated around the tip of the implant; RPE = Retinal pigment epithelium.

Table 8: Ophthalmic Examination Findings in Right Eyes Administered Multiple Doses of Ranibizumab via RPDS

Finding	Study Day 15	Study Day 29	Study Day 43	Study Day 57	Study Day 71	Study Day 85	Study Day 99	Study Day 113	Study Day 127	Study Day 141	Study Day 155	Study Day 169	Study Day 176
Keratic Precipitates	-	-	-	-	-	-	-	1	-	-	-	-	-
Aqueous Flare													
Trace	-	-	-	-	-	-	-	1	-	-	-	-	-
1+	-	-	-	-	-	-	-	-	-	-	-	-	-
2+	-	-	-	-	-	-	1	-	-	-	-	-	-
Aqueous Cell													
Trace	-	-	-	-	-	-	-	1	-	-	-	-	-
1+	-	-	-	-	-	-	-	-	-	-	-	-	-
2+	-	-	-	-	-	-	1	-	-	-	-	-	-
Incomplete pupil dilation	-	-	-	-	-	-	1	1	-	-	-	-	-
Vitreous Cell													
0.5	-	-	1	-	-	-	-	-	1	-	2	1	1
1	-	-		-	-	-	1	1	-	1	1	-	-
2	-	-	-	-	-	1	-	-	3	2	-	2	2
3	-	-	1	-	2	3	3	4	1	1	1	-	-
4	3*	3	3	4	3	1	1	-	-	-	-	-	-
Inflammatory Debris Lens Capsule	-	-	-	-	-	-	1	1	-	-			
Vitreous Haze													
0.5	-	-	-	-	-	1	-	2	2	2	-	-	1
1	-	-		-	2	2	2	-	1	-	-	1	-
2	1	-	1	1	2	1	1	2	-	1	1	-	1
3	-	1	-	2	1	-	-	-	-	-	-	-	-
4	3	3	2	2	-	-	-	-	-	-	-	-	-
Fundus Degraded View- Severe	3	1	-	-	-	-	-	-	-	-	-	-	-
Blood on Implant	3	1	-	-	-	-	-	-	-	-	-	-	-

- = Finding not present at this interval; * = some were also red in color.

Finding	Study Day 15	Study Day 29	Study Day 43	Study Day 57	Study Day 71	Study Day 85	Study Day 99	Study Day 113	Study Day 127	Study Day 141	Study Day 155	Study Day 169	Study Day 176
Fibrin/Exudate in Vitreous or Over Implant	4	4	4	4	4	3	3	1	1	1	-	-	-
White Vitreous Floater	1	-	-	-	2	3	3	4	1	1	1	2	3
White Floater Distorts Retina	-	-	-	-	-	-	-	1	-	-	-	1	1
Retinal Perivascular Sheathing	-	-	-	-	-	-	-	-	1	-	-	-	-
Cataract Secondary to Implant	-	-	-	-	-	-	-	1	-	-	-		1

- = Finding not present at this interval; * = some were also red in color.

Intraocular Pressure (Predose, Days 29, 57, 85, 113, 141,169, and 176, and Days 29, 57, 85, 113, 141, and 169 prior to refill procedure)

No test article-related effects

Ocular Photography, Fluorescein Angiography (FA), and Optical Coherence Tomography (OCT) – Fundus (Predose and Weeks 13 and 26)

- No adverse structural effects were noted on OCT, fundus imaging or FA in vehicle-filled implant control.

- In the single-dose and multiple-dose ranibizumab filled implants, on OCT, fundus photography, and FA, ocular inflammation correlated with hazy media, perivascular sheathing, epiretinal membrane formation, venous dilation, vascular fluorescein leakage, capillary micro-aneurysms, optic nerve swelling, and increased hyper reflective spots in the vitreous.
- More extensive right eye fundus abnormalities were noted in several animals administered multiple doses of ranibizumab via RPDS.
- Vitreous optic nerve traction or retinal detachment was only observed in eyes administered multiple doses of ranibizumab via RPDS.
- The findings are shown in Tables 9 to 11.
- These findings correlated with presence of ATA, supporting the view of an immune-mediated response.

Table 9: Individual Color Photography Findings

Animal	Group/	Study	Hazy Media		Vitreous-Optic Nerve Traction		Perivascular Sheathing		Implant Visible		Epiretinal Membrane		Traction Retinal Detachment		Optic Nerve Swelling	
Number	Sex	Day	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS
M03395	1/F	DP 90							X							
M03396	1/F	DP 90							X							
M03397	1/F	DP 182							X							
M03398	1/F	DP 90							X							
M03399	1/F	DP 90							X							
M03400	2/F	DP 90					X		X							
		DP 182	X				X									
M03401	2/F	DP 90	X													
		DP 182									X					
M03404	2/F	DP 90	X				X		X							
		DP 182					X				X					
M03402	3/F	DP 90							X							
		DP 182							X							
M03405	3/F	DP 90	X													
		DP 182	X				X		X				X		X	
M03406	3/F	DP 90	X						X							
M03407	3/F	DP 90	X				X								X	
		DP 182			X		X				X				X	
M03408	3/F	DP 90							X							
		DP 182			X		X									
M30410	3/F	DP 90	X						X							

OD = Right eye.
OS = Left eye.
DP = Dosing Phase.
X = Present.

Table 10: Individual Fluorescein Angiography Findings

Animal Number	Group/ Sex	Study Day	Hazy Media		Marked Vascular Leakage		Microaneurysms		Mild Vascular Leakage		Moderate Vascular Leakage		Venous Dilation		Implant Visible		Mild Venous Bleeding	
			OD	OS	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS
M03395	1/F	DP 90													X			
M03396	1/F	DP 90													X			
M03398	1/F	DP 90													X			
M03400	2/F	DP 90									X		X		X			
		DP 182	X								X							
M03401	2/F	DP 90	X						X									
		DP 182							X									
M03404	2/F	DP 90	X								X				X			
		DP 182					X											
M03402	3/F	DP 90													X			
M03405	3/F	DP 90	X														X	
		DP 182	X				X				X							
M03406		DP 90	X															
M03407	3/F	DP 90	X		X													
M03410	3/F	DP 90	X								X							

OD = Right eye.
OS = Left eye.
DP = Dosing Phase.
X = Present.

Table 11: Individual Qualitative OCT Findings

Animal Number	Group / Sex	Study Day	Hazy View		Poor View/ Shadowing		Increased hyper reflective spots		Optic nerve swelling		Perivascular sheathing		Retinal detachment		Epiretinal membrane (ERM)	
			OD	OS	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS
M03398	1/F	Week 13	X													
M03400	2/F	Week 13			X						X					
		Week 26			X		X		X		X					
M03401	2/F	Week 13			X		X								X	
		Week 26													X	
M03404	2/F	Week 13			X		X		X		X					
		Week 26			X		X		X		X				X	
M03405	3/F	Week 13			X		X		X						X	
		Week 26			X		X		X		X		X		X	
M03406	3/F	Week 13			X											
		Week 26			X											
M03407	3/F	Week 13			X				X							
		Week 26			X		X		X		X					
M03408	3/F	Week 13			X		X									
		Week 26							X		X		X		X	
M03409	3/F	Week 13					X				X					
		Week 26					X				X					
M03410	3/F	Week 13			X		X		X		X					

OD = Right Eye.
OS = Left Eye.
X = Present.

Full-Field Electroretinography (Scotopic, photopic, and VEP tests; predose and Weeks 13 and 26)

No test article-related effects

Hematology and Coagulation (Predose and Weeks 13 and 26)

No test article-related effects

Clinical Chemistry (Predose and Weeks 13 and 26)

No test article-related effects

Gross Pathology (Day 183)

No test article-related findings

Organ Weights (Adrenals, brain, gall bladder, heart, kidney, liver, lung/large bronchi, ovary, pituitary gland, mandibular salivary gland, spleen, thymus, thyroid, uterus)

No test article-related effects

Histopathology (Eye with bulbar conjunctiva, optic Nerve, full list of systemic tissues)

Adequate Battery: Yes

Peer Review: Yes

Histological Findings

- Sham surgeries and vehicle control implants were associated with minimal or slight infiltrates of lymphocytes/macrophages adjacent to the surgery site.
- In control animals, the right upper palpebral conjunctiva (the eye administered the vehicle in RPDS) had minimally to slightly increased mixed (inflammatory) cell infiltrates compared with the left upper palpebral conjunctiva (the sham-surgery eye) (Table 12). The mixed cell infiltrate was characterized by the presence of neutrophils, lymphocytes, and macrophages.

Table 12: RPDS Implant-Related Findings in Animals Administered Vehicle Control Article

	Group 1	
	Vehicle in RPDS (Right Eye)	Not Dosed; (Sham; Left Eye)
Upper palpebral conjunctiva		
Number examined	5	5
Infiltrate, neutrophils		
Not present	5	4
Minimal	0	1
Infiltrate, mixed cell		
Not present	1	5
Minimal	3	0
Slight	1	0
Lower palpebral conjunctiva		
Number examined	4	5
Infiltrate, neutrophils		
Not present	3	5
Minimal	1	0

RPDS = Ranibizumab Port Delivery System.

- In eyes treated with ranibizumab via RPDS, increased incidence and severity of infiltrates of lymphocytes/macrophages, infiltrates of plasma cells and increased severity of peri-RPDS implant inflammatory cells and fibrosis were observed (Table 13).
    - One single-dose animal (# M03400) had retinal degeneration characterized by an increased number of 'dropped down' photoreceptor nuclei. This animal had plasma cells in the retina/optic disk, vitreous and anterior chamber.
    - Another single-dose animal (# M0340) had plasma cells in retina/optic disk, but no retinal degeneration.
- Microscopic findings related to multiple administrations of ranibizumab included retinal detachment/folding with optic disc swelling (animal # M03505 and # M03410 [euthanized early]), and photoreceptor nuclei drop down (animal # M03410).
    - In these animals with retinal findings, plasma cells were present in the retina/optic disk and vitreous.
    - Another multiple dose animal (# M03409) had plasma cells present in the retina/optic disk but no retinal findings.

Table 13: Microscopic Observations in Ranibizumab RPDS

	Group 2		Group 3	
	One Dose of Ranibizumab		Multiple Doses of Ranibizumab	
	Ranibizumab in RPDS (Right Eye)	Not Dosed (Sham; Left Eye)	Ranibizumab in RPDS (Right Eye)	Not Dosed (Sham; Left Eye)
Number examined	3	3	7	7
Eyes (Left/Right)				
Infiltrate, lymphocytes/ macrophages				
Not present	0	3	0	2
Minimal	0	0	4	5
Slight	3	0	2	0
Moderate	0	0	1	0
Infiltrate, plasma cells				
Not present	0	3	1	7
Minimal	2	0	0	0
Slight	1	0	5	0
Moderate	0	0	1	0
Infiltrate, neutrophils, vitreous				
Not present	2	3	4	7
Minimal	1	0	2	0
Slight	0	0	1	0
Infiltrate, mixed cell				
Not present	3	3	6	7
Marked	0	0	1	0

RPDS = Ranibizumab Port Delivery System.

- Peri-implant fibrosis was noted in eyes of all groups (vehicle control article, ranibizumab via RPDS without refill, and ranibizumab via RPDS with multiple refills). The peri-implant fibrosis was attributed by the pathologist to an apparent instability of the implants within the wall of the eye. Microscopically, many implants appeared not to be lodged within the sclera on one side. No evidence of tissue breakdown (erosion) was found. The fibrosis was indicative of healing (scar tissue).
- Administration of multiple doses of ranibizumab via RPDS was associated with an increased severity of peri-RPDS implant fibrosis and peri-RPDS implant inflammatory cell presence (Table 14).
    - The increase in inflammatory cell infiltrates, especially the presence of plasma cells, was consistent with an immune mediated response to ranibizumab via RPDS.
    - This finding also correlated with ocular inflammation noted during ophthalmic examinations and ocular imaging.
    - The increased severity of peri-implant fibrosis with repeated doses of ranibizumab suggests some component of the fibroplasia was exacerbated by ranibizumab.

Table 14: Microscopic Observations Adjacent to Ranibizumab Port Delivery System (RPDS) Implants

	Group 1	Group 2	Group 3
	Vehicle in RPDS	One Dose of Ranibizumab	Multiple Doses of Ranibizumab
Number Examined	5	3	7
Eye, Right			
Fibroplasia, Peri-RPDS implant			
Not present	0	0	0
Minimal	3	1	0
Slight	2	2	4
Moderate	0	0	3
Inflammatory cells NOS, Peri-RPDS implant[a]			
Not present	1	0	0
Minimal	3	2	0
Slight	1	1	6
Marked	0	0	1

NOS = Not otherwise specified; RPDS = Ranibizumab Port Delivery System.
a These observations were made from sections containing implants for which microscopic detail was insufficient to accurately differentiate inflammatory cell lines

- Per conclusions in the Study Report, all ranibizumab via RPDS-related ophthalmologic and histological findings were consistent with an immune-mediated response to a foreign protein.
  - Individual animal listings showed all Group 2 and Group 3 animals had plasma cells in the eye except for animal # M03402 with lower ATA titer (see below). The findings in this one animal with no plasma cells were consistent with those observed in animals treated with vehicle-filled implant control (without ranibizumab) and considered procedure and/or implant (alone) related (see histopathology findings in this animal in Table 15).
  - Overall, this reviewer agrees the data support the immunogenic reaction conclusion.

Table 15: Histopathology Findings in the Single Animal without Plasma Cells in the Eye and Lower Serum ATA Titer

Animal Number: M03402	Group: 3	Sex: F	Fate Status: Terminal Sacrifice
Date of Fate: 15 Jul 15	Phase of Fate: Dosing	Phase Wk/Day of Fate: 27/183	TBW(g): 22500.0

Macroscopic Observation(s)	Microscopic Observation(s)
	Eye, Left: Fibroplasia, sham surgery site; slight Eye, Left: Sham surgery site; Present Eye, Right: Fibroplasia, peri-implant; moderate Eye, Right: Foreign material (sutures) peri-implant; Present Eye, Right: Infiltrate, lymphocytes/macrophages; minimal; multifocal Eye, Right: Infiltrate, neutrophils, vitreous; minimal Eye, Right: Inflammatory cells NOS, peri-implant; slight Eye, Right: TISSUE COMMENT: Peri-implant fibroplasia is around the base of the implant where it passes through the wall of the eye and extends in a thin layer partway along the outer surface of the implant. Peri-implant inflammatory cells are round the base of the implant. Infiltrate, lymphocytes/macrophages present in the vitreous and choroid.

Toxicokinetics - Blood samples collected at the intervals shown in the following table:

Group(s)	Interval (Study Day) / Time Points[a]
1, 2, 3	Predose: Within 1 week prior to Study Day 1
1, 2, 3	Study Day 1: Approximately 6 hours postdose
2	Study Days 4, 7, 11, 14, 28, 58, 72, 87, 116, 145, and 183: Once
1, 3	Study Days 4, 7, 11, 14, 28, 43, 56, 71, 84, 99, 112, 127, 140, 155, 168, and 183: Once
1, 3	Study Days 29, 57, 85, 113, 141, and 169: Approximately 1 and 6 hours postdose

a See Protocol Deviations.

Single ranibizumab dose (Group 2 and first dose of Group 3): Ranibizumab was detected in the serum for up to Day 27 in animals given a single dose. After administration of a single dose (Group 2 and first dose in Group 3), ranibizumab mean T_{max} values were 27.0 days for Group 2 and 20.9 days for Group 3. Ranibizumab levels were below the lower limit of quantitation (<0.350 ng/mL) from Day 58 evaluations onward in all single-dose (Group 2) animals.

Multiple ranibizumab doses (Group 3): In multiple-dose animals, ranibizumab levels below the lower limit of quantitation (<0.350 ng/mL) were observed in 4 animals on Day 42 (with sporadically showing low levels at some later timepoints) and in all but one animal (# M03402) on Day 126 (15 days after the 5^{h} dose). The presence of ATA reduced the serum concentrations of ranibizumab in most animals. Only animal # M03402 had quantifiable levels of ranibizumab throughout the study (≤19.4 ng/mL), which was the animal with lower ATA titer (2.66 vs 4.36 to 5.24 titer units in all other animals on Day 183).

After 7 monthly doses, ranibizumab accumulation ratio over the first dose was 15.3 and 20.5 for C_{max} and AUC, respectively, in animal # M03402 (the only animal with quantifiable levels of ranibizumab at end of study).

The mean and individual serum concentrations are shown in Table 16 and 17 below, respectively.

Table 16: Mean Toxicokinetic Parameters for Ranibizumab in Female Minipig Serum

Dose Group	Dose Level (mg/eye/dose)	C_{max} First Dose (ng/mL)	C_{max} Last Dose (ng/mL)	AUC_{0-13} (ng·day/mL)	AUC_{0-27} (ng·day/mL)	AUC_{0-182} (ng·day/mL)	$AUC_{168-182}$ (ng·day/mL)
2	2.3	2.10	NA	9.43	31.7	NA	NA
3	2.3	1.73	19.4[a]	9.11	38.8	838	231[a]

Note Group 2 was administered Ranibizumab as a single dose on TK Day 0. Group 3 was administered Ranibizumab once monthly.
NA Not applicable.
a Not a true mean as N=1.

Table 17: Individual Animal Data for RPDS (Group 3) Animals Showing BLQ Ranibizumab Levels with Increase Number of Refills

Dose Group	Dose Level (mg/eye/dose)	Animal Number	Time After Dose (day) 0	0.25	3	6	10	13	27	28.0417	28.25	42	55	56.0417	56.25
3	2.3	M03402	BLQ	0.787	0.602	0.864	1.03	1.13	1.27	14.1	4.04	1.40	2.53	5.22	4.29
		M03405	BLQ	BLQ	0.436	0.700	0.564	0.822	2.14	8.22	5.87	BLQ	BLQ	0.518	BLQ
		M03406	BLQ	BLQ	BLQ	0.499	0.523	0.869	0.370	0.916	0.442	BLQ	BLQ	BLQ	BLQ
		M03407	BLQ	BLQ	BLQ	0.689	1.01	1.05	2.49	3.58	1.72	BLQ	BLQ	1.99	1.71
		M03408	BLQ	BLQ	0.424	0.618	0.967	1.15	2.68	5.91	7.02	4.03	3.39	18.5	28.6
		M03409	BLQ	BLQ	0.574	0.586	0.689	1.02	1.92	2.45	2.95	5.91	3.77	5.31	4.96
		M03410	0.973	BLQ	BLQ	0.364	0.623	1.85	BLQ	11.6	41.9	BLQ	BLQ	BLQ	4.12
		M03411	BLQ	BLQ	0.496	0.602									
		Mean	0.973	0.787	0.506	0.615	0.772	1.13	1.81	6.68	9.13	3.78	3.23	6.31	8.74
		SD	NA	NA	0.0799	0.147	0.222	0.342	0.861	4.88	14.6	2.27	0.635	7.12	11.2
		CV%	NA	NA	15.8	24.0	28.7	30.3	47.5	73.0	160	59.9	19.7	113	128

Dose Group	Dose Level (mg/eye/dose)	Animal Number	Time After Dose (day) 70	83	84.0417	84.25	98	111	112.0417	112.25
3	2.3	M03402	3.83	3.41	9.74	6.35	6.44	7.26	8.09	10.3
		M03405	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
		M03406	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
		M03407	BLQ	BLQ	1.85	1.45	BLQ	BLQ	BLQ	BLQ
		M03408	0.686	0.749	1.87	1.86	BLQ	0.363	1.31	1.15
		M03409	2.29	1.67	3.60	5.46	BLQ	BLQ	2.05	2.49
		M03410	BLQ	BLQ	16.7	59.4	BLQ	BLQ	0.432	37.6
		Mean	2.27	1.94	6.75	14.9	6.44	3.81	2.97	12.9
		SD	1.57	1.35	6.44	25.0	NA	NA	3.48	17.0
		CV%	69.3	69.5	95.3	168	NA	NA	117	132

Dose Group	Dose Level (mg/eye/dose)	Animal Number	Time After Dose (day)								
			126	139	140.0417	140.25	154	167	168.0417	168.25	182
3	2.3	M03402	11.4	16.7	15.6	15.8	23.1	18.5	16.4	19.4	13.6
		M03405	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	UTO	BLQ	BLQ
		M03406	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
		M03407	BLQ	BLQ	0.968	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
		M03408	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
		M03409	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
		Mean	11.4	16.7	8.28	15.8	23.1	18.5	16.4	19.4	13.6
		SD	NA	NA	NA	NA	NA	NA	NA	NA	NA
		CV%	NA	NA	NA	NA	NA	NA	NA	NA	NA

Note Animals were dosed monthly.
BLQ < 0.350 ng/mL
NA Not applicable.
UTO Unable to obtain.

Anti-therapeutic Antibody (ATA) Analysis - Blood samples collected at the intervals shown in the following table:

Group(s)	Interval (Study Day) / Time Points
1, 2, 3	Predose: Within 1 week prior to Study Day 1
2	Study Days 7, 14, 28, 58, 87, 116, 145, and 183: Once
1, 3	Study Days 7, 14, 28, 56, 84, 112, 140, 168, and 183: Once

ATA were detected in all animals (10/10) administered ranibizumab via RPDS.

- In Group 2, no animal (0/3) was positive at baseline; 1 of 3 animals were positive on Day 14, and 3/3 animals were positive on Days 28 through Day 183.
- In Group 3, no animals were positive at baseline; 2 of 7 were positive on Day 14, 6 of 7 animals were positive on Day 28, and all seven were positive on Day 56 through Day 183.
- Titers had not decreased by Day 183 (end of study).

Dosing Solution Analysis:

The formulations were used as supplied. Concentration verification was not performed because certificate of analyses was used to support doses delivered.

7 Genetic Toxicology

No studies have been conducted with ranibizumab. In accordance with ICH Guidance for Industry S6(R1), genotoxicity studies are not applicable to biotechnology-derived pharmaceuticals.

The implant was considered non-mutagenic based on negative in vitro bacterial reverse mutation assay (Study 14-0447) and in vitro mouse lymphoma genotoxicity assay (Study 14-0448) conducted as part of biocompatibility testing. The extracts from the implant (sterilized and packaged) were employed as the test article, consistent with ISO 10993-3. The biocompatibility studies were reviewed by CDRH team (see consult review by Simona Bancos, PhD, filed in DARRTS by Diana M Willard, Project Manager, on 6-22-2021).

8 Carcinogenicity

Long-term studies in animals to evaluate carcinogenic potential of ranibizumab have not been performed. Per ICH S6 guidance, standard carcinogenicity studies are generally not appropriate for biotechnology-derived pharmaceuticals.

No carcinogenicity studies have been conducted with the implant based on negative in vitro genotoxicity results with implant extracts, the lack of potentially genotoxic extractables, and consistent with ISO 10993-1. See CDRH consult review cited above for further details.

9 Reproductive and Developmental Toxicology

No reproductive and developmental toxicity studies with the implant have been conducted (in accordance with ISO 10993-1). The 6-month necropsy findings from the GLP PDS toxicity study in minipigs (Study # 14-2350) and ocular implantation toxicity study in rabbits (Study # 14-0137) did not identify any macroscopic or microscopic abnormalities in reproductive organs in sexually mature animals.

For BLA 125156 (Lucentis®), Genentech conducted an embryofetal developmental toxicity study (Study # 08-0590) with ranibizumab administered via IVT injection in pregnant cynomolgus monkeys. Pregnant monkeys received bilateral IVT injections of ranibizumab every 14 days starting on Day 20 through Day 62 of gestation at a dose of 0, 0.125, and 1.0 mg/eye. Genentech is using this study for the current BLA label with exposure margins corrected for the ranibizumab serum levels observed in patients treated with PDS 100 mg/mL.

The Applicant calculated exposure margins using a human serum C_{max} of 1.1 ng/mL (geometric mean) observed in patients treated with PDS 100 mg/mL in Phase 2 Study GX28228 (Ladder). In this study, ranibizumab via the PDS was administered PRN (not at the intended dosing regimen of Q24W). The serum concentrations observed in the monkey embryofetal developmental toxicity study (Study # 08-0590) are shown in the table below (excerpted from nonclinical review for Lucentis® BLA 125156/s69 (SD # 28), Janice Lansita, PhD.

Table 18: Serum Ranibizumab Concentrations (pg/ml) in Pregnant Monkeys following Bilateral Intravitreal Administration of 0.125 mg/eye on Gestation Days (GD) 20, 34, 48, 62

Dose Group	GD 20	GD 21	GD 34	GD 35	GD 48	GD 49	GD 62	GD 63
0 mg/eye	LTR	LTR	LTR	LTR	LTR	LTR	LTR	LTR
0.125 mg/eye	LTR	18,138	410	16,491	315	17,182	331	18,850
1.0 mg/eye	LTR	136,600	3,781	130,550	6,203	194,894	19,819	420,275

LTR: less than reportable, 75 pg/ml

Based on a human C_{max} of 1.1 ng/mL, the trough concentrations at 1.0 mg/eye (LOAEL) in the monkey were 3.4- to 18-fold higher than clinical C_{max} value. The exposure margins are 0.29 to 0.37-fold at the NOEL of 0.125 mg/eye. However, this reviewer has some observations regarding the human C_{max} values to use for exposure margin calculations in the BLA:

- The Applicant calculated the exposure margin at the high dose of 1.0 mg/eye as 17-fold (see page 14, Pharmacokinetics Written Summary) vs 18-fold by this reviewer.
- The Applicant calculated the exposure margins at the low dose of 0.125 mg/eye based on trough serum ranibizumab levels observed in a different clinical trial, i.e., Phase 3 Study GR40548 (Archway), where the median serum ranibizumab concentration was 330 pg/mL. Therefore, the Applicant stated: *"At the lower dose of 0.125 mg/eye, mean serum trough levels ranged from 315 to 410 pg/mL, similar to the trough serum ranibizumab levels observed in patients treated with PDS 100 mg/mL refilled with ranibizumab Q24W in pivotal Phase III Study GR40548 (Archway), where the PK evaluable population had a median serum ranibizumab concentration of 330 pg/mL."* Phase 3 Study GR40548 is the clinical trial with the same dosing regimen as intended for marketing.
- In the proposed label, it is stated: " (b) (4)
- P/T usually calculates exposure margins based on the PK data on Section 12.3 of the label. In conversations with the Clinical Pharmacology team, a decision was reached that the most appropriate clinical exposure value to use is the arithmetic mean from pivotal Phase III Study GR40548 (same dosing regimen as intended for marketing). (b) (4)
- As shown in Table 4, 2.7.2 Summary of Clinical Pharmacology Studies, page 24, copied below, the C_{max} values in this study were 0.48 ng/mL (arithmetic mean) and 0.45 ng/mL (geometric mean).

- The exposure margins calculated by this reviewer using the arithmetic mean are shown in the following table:

Table 19: Exposure Margins for Embryofetal Development Data

Regimen	Dose (mg/eye)	C_{max} range (pg/mL)	Exposure margin (based on human $C_{max\ of}$ 0.48 ng/mL)*
PDS in humans	2	480*	--- ---
Monkey, IVT Q14D	0.125 (NOEL)	315 to 410	0.66 to 0.85
	1.0 2.0 (LOAEL)	3781 to 19819	7.9 to 41.2

*Arithmetic mean (0.48 ng/mL) in Phase 3 Study GR40548
This table was generated by this reviewer.

Table 4 Summary of Serum Ranibizumab PK Parameters for Patients in the PDS 100 mg/mL arm from Selected Sites with Additional PK Sampling in the PK-Evaluable Population, Study GR40548

	C_{max} (ng/mL)	T_{max} (day)	C_{min} [a] (ng/mL)	$AUC_{0\text{-}168\ Day}$ (day.ng/mL)	$t_{1/2}$ [b] (day)
n	29	29	29	29	5
Mean (SD)	0.48 (0.17)	28.45 (28.24)	0.31 (0.08)	59.48 (18.99)	537.95 (273.75)
CV% Mean	35.5	99.3	26.0	31.9	50.9
Geometric Mean	0.45	11.38	0.30	56.27	482.22
CV% Geometric Mean	34.2	467.3	29.7	37.0	57.7
Median (Min - Max)	0.45 (0.2 - 1.0)	26.06 (0.8 - 88.8)	0.31 (0.1 - 0.5)	59.50 (18.3 - 117.7)	469.95 (225.3 - 950.2)

$AUC_{0\text{-}168Day}$ = area under the concentration-time curve from 0 to 168 days; C_{max} = maximum serum concentration; C_{min} = minimum serum concentration; $t_{½}$ = half-life; T_{max} = time of maximum concentration
Note: Due to a numerical error from the source document, $AUC_{0\text{-}128\ Day}$ has been changed to $AUC_{0\text{-}168\ Day}$ in this document.
[a]: same as C_{trough}
[b]: apparent terminal half-life
Source: GR40548 Update CSR: Table 17

- The clinical mean C_{max} observed with the RPDS was lower than that observed with Lucentis®. Language in the approved Lucentis® label states: *"In patients with neovascular AMD, following monthly IVT administration of 0.5 mg LUCENTIS, mean (±SD) maximum ranibizumab serum concentrations were 1.7 (± 1.1) ng/mL."*

- The clinical C_{max} (mean of 0.48 ng/mL) observed with RPDS in Phase 3 Study GR40548 is below K_D values for VEGF isoforms (K_D range of 99 to 260 pM or 4.8 to 12.6 ng/mL), although the same observation applies for IVT Lucentis®.
- The lower clinical serum concentration supports lower risk with RPDS.

10 Special Toxicology Studies

The following studies were previously submitted to IND 113552 and reviewed by Ilona Bebenek, PhD.

6-Month Ocular Study with Scaled Nonfunctional Polysulfone (b) (4) Port Delivery System in Male and Female New Zealand White Rabbits (Study # 14-0137) (Interim Final Study Report submitted with the Initial IND, nonclinical review filed in DARRTS on 7-6-2015; final report submitted under SD # 13, nonclinical review filed in DARRTS on 8-26-2015)

Twelve male and female New Zealand White rabbits were injected with a nonfunctional (b) (4) PDS (surrogate; no drug) in the right eye and underwent sham surgery in the left eye. In addition, six male and female New Zealand White rabbits underwent a sham surgery in the left eye while the right eye was left untreated. The implants were non-functional and scaled to one-third size to match the smaller size of the rabbit eye.

Key findings, per Dr. Bebenek's review included:

- The scaled nonfunctional polysulfone (b) (4) PDS was well tolerated through Day 180 with procedure-related ophthalmic examination findings in implanted eyes comparable to those seen in sham-operated eyes.
- Clinical signs included transiently red and swollen conjunctiva at similar frequency between the sham and implanted eyes.
- Mild to moderate hyperemia, chemosis and mucoid ocular discharge were transiently present in both sham and implant eyes, and subsided after about 30 days; these effects were less frequently encountered in eyes of animals with sham surgery in the left eye and untreated right eye.
- One implant was found extruded by Day 90 and one was partially extruded by the end of the study, in a separate animal.
    - Extrusion of the implant was considered related to the fact that the dimensions of the non-functional scaled implant was not optimized for the rabbit sclera (the same reason was provided for extrusion observed in the 2-month pilot study).
- Microscopic findings appeared related to the surgical procedure rather than the implant itself except for minimal fibrosis, which was only noted in two out of eight implanted eyes. In one eye, the fibrosis was accompanied by very small numbers of mixed inflammatory cells and multinucleated giant cells.

A 2-Month Pilot Ocular Tolerability Study with a Nonfunctional Polysulfone (b) (4) Port Delivery System (Surrogate Kit 106-411-052) in Female New Zealand White Rabbits (Study #13-1963; non-GLP) (Initial IND nonclinical review filed in DARRTS on 7-6-2015)

Implants were scaled down to one-third size to match the smaller size of the rabbit eye. Five female New Zealand White rabbits were implanted with a nonfunctional polysulfone device to the right eye and sham surgery was performed on the left eye. Animals were sacrificed on Day 57.

Key findings, per Dr. Bebenek review included:

- One animal was sacrificed on Day 3 due to findings of the right eye during the ophthalmic observation. The findings included severe white vitreous cell, moderately severe conjunctival hyperemia, moderate chemosis, mild iris hyperemia, incomplete pupil dilation and mild vitreous haze. The implant was not located in the right eye (never located) and probably extruded, and secondary bacterial endophthalmitis could not be excluded.
- Other findings in the remaining animals included ocular irritation (at same frequency between the two eyes). Conjunctival hyperemia, chemosis and ocular discharge resolved by Day 29/30 (after dissolution of conjunctival sutures).
- Of the five animals that underwent implantation, the implant was extruded in two eyes (including the implant that was extruded on Day 3). The other extruded implant was located in the subconjunctival space (at some point before Day 15). The extrusions were attributed to the size of the incision or the design of the scaled-down implant.
- Microscopic findings at the implantation site were similar to those at the sham implantation site and were considered related to the surgical procedure and not considered reflective of any abnormal response to the device.

Biocompatibility testing (Studies under Module 4.2.3.6 Local Tolerance)

A comprehensive biocompatibility testing of the implant and four ancillary devices (insertion tool assembly, initial fill needle, refill needle, and explant tool) was conducted. These studies were reviewed by the CDRH team.

11 Integrated Summary and Safety Evaluation

The nonclinical PDS program focused on the safety of the combination of the PDS implant with ranibizumab or the implant alone as well as a comprehensive battery of biocompatibility testing for the implant and ancillary devices. The safety and efficacy of ranibizumab were characterized extensively in nonclinical and clinical studies using IVT injection for approval of BLA 125156 (Lucentis®, Genentech, approved 2006).

The Yucatan minipig was selected as the appropriate species to assess PDS chronic toxicity and toxicokinetics because the eyes of the original toxicology species (rabbit and cynomolgus monkey) are too small to accommodate the full-scale clinical implant. Although no functional data was submitted to support species relevancy, the Applicant noted that (1) porcine VEGF is more than 90% homologous with human VEGF by DNA sequence and is predicted to differ from human VEGF by five amino acids[2] and (2) the contact residues for ranibizumab binding to VEGF are conserved between human macaques, and pigs[3].

A study comparing ranibizumab levels in the vitreous and serum was conducted in minipigs following RPDS insertion or IVT ranibizumab. A 6-month ocular tolerability study of the RPDS was conducted in minipigs.

New Zealand White rabbits were used as an appropriate species to assess long-term tolerability of the PDS implant (no ranibizumab). Surrogate PDS implants, designed for use in rabbits, were made from the same materials used in the manufacture of the PDS implant, but they were non-functional and scaled one-third size to match the smaller size of the rabbit eye.

Comparative PK Data in Minipigs: RPDS vs IVT Ranibizumab

The study showed that following a single IVT injection of Lucentis (0.5 mg/eye), there was continuous exposure for at least 18 days (last timepoint evaluated). Ranibizumab levels were observed at a maximum on Day 5 (the first vitreous timepoint sampled). On Study Day 12, the concentrations had declined, but were still quantifiable on Study Day 18 (last timepoint sampled).

In animals treated with the RPDS, ranibizumab vitreous levels were measured at a single timepoint, i.e., 2 weeks after the refill dose administered on Day 46. Although the study design does not allow for a full side-to-side comparison of vitreous levels between IVT injection and RPDS implant because of limited PK sampling in RPDS-treated animals, ranibizumab concentrations in the vitreous were comparable to those observed after IVT injection at a similar timepoint (i.e., Days 12 and 18 postdose).

The serum PK profile in animals with the RPDS was consistent with continuous delivery of ranibizumab from the implant. However, the serum concentrations appeared to exhibit a biphasic pattern. The Applicant hypothesis is that the increase in ranibizumab serum exposure may be attributable to ATAs acting as carrier proteins for ranibizumab,

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[2] Sharma HS, Tang ZH, Gho BC, et al. Nucleotide sequence and expression of the porcine vascular endothelia growth factor. *Biochimica et Biophysica Acta* 1995;**1260(2)**: 235-238.

[3] Heckel T, Schmucki R, Berrera M, et al. Functional analysis and transcriptional output of the Gottingen minipig genome. *BMC Genomics* 2015;**16**: 932-950.

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 (Study # 14-2350, see below). The ATA response led to decreased serum concentrations with each monthly refill dose 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 clinic.

This reviewer agrees that despite the fact that serum concentrations after Day 15 were confounded by the presence of serum ATAs, the serum PK profile shows the PDS continuously delivered ranibizumab over an extended period of time. Comparative data at the same timepoints showed 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 C_{max} range observed with IVT injection.

The continuous release observed in vivo from the RPDS (up to 61 days in this study) is consistent with continuous release observed in in vitro studies using PBS or human vitreous (for up to 6 months).

Tolerability of the Surrogate PDS Implant (no ranibizumab) in Rabbits

In rabbit studies of up to 2-month and 6-month duration with the PDS 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.

Findings included transient conjunctival hyperemia and chemosis (mild to moderate) and mucoid ocular discharge (mild to moderate), very small numbers of mixed inflammatory cells and multinucleated giant cells, and minimal fibrosis (in eyes with the implant).

The implant extruded in 2 of 5 eyes in the 2-month study and in 2 of 24 eyes (one partially) in the 6-month study. The implant movement was considered due to anatomical differences in scleral thickness and shape of the globe at the implantation site. However, implant dislocation was also observed in the clinical trials.

Pivotal 6-Month RPDS Ocular Toxicity Study in Minipigs

In the pivotal 6-month RPDS ocular toxicity study in minipigs, implant-related findings (with or without ranibizumab) included varying amounts of blood on the surface of the implant, red vitreal floaters (vitreous hemorrhage), white vitreous floaters, and yellow reddish material which appeared to be fibrin and blood throughout the vitreous, yellow-white exudate around the implant, vitreous haze, and implant protrusion/extrusion above the sclera. The implant movement was considered due to anatomical differences between porcine and human eye. As noted above, implant dislocation was also observed in the clinical trials. These ophthalmic findings decreased by Day 29 and resolved without consequence by Day 71 in most eyes. Fibrosis over the implant surface was observed microscopically.

Administration of a single dose (2.3 mg, no refill) or multiple doses (monthly refills of 2.3 mg for a total of 7 doses) of ranibizumab via RPDS was associated with increased severity of ocular inflammation, resulting in unscheduled euthanasia for one animal after administration of the 5th monthly dose. The inflammation correlated with optical coherence tomography, fundus photography, and fluorescein angiogram findings of perivascular sheathing, epiretinal membrane formation, venous dilation, vascular leakage, capillary microaneurysms, optic nerve swelling, and increased hyper-reflective spots in the vitreous. Vitreous optic nerve traction or retinal detachment was observed only in eyes receiving multiple doses of ranibizumab administered via the implant.

All ranibizumab-related findings were considered related to an immune-mediated response to a foreign protein, which was supported by findings of infiltrates of lymphocytes/macrophages and plasma cells, perivascular sheathing, and systemic ATA presence.

A NOAEL was not determined in the study. Immunogenicity in animals may or may not be predictive of a similar effect in humans. Per information in the proposed label (Section 6.2 Immunogenicity), after the RPDS implant insertion and treatment, ATAs were developed in 12% (29 of 247) patients. In previously treated nAMD patients, ATAs were detected in 2.1% (5 of 243) prior to insertion of the implant. The Applicant stated that no safety signal relating to intraocular inflammation has been observed to date with the pivotal clinical PDS data (see Module 2.6.6 Toxicology Written Summary, page 6 and 25). Per proposed label, the RPDS was associated with a higher rate of endophthalmitis compared to monthly IVT injections of ranibizumab. Most of these events were associated with conjunctival retractions or erosions. Therefore, the endophthalmitis appears procedure related.

No systemic toxicities were observed in the minipig. The ATA response resulted in reduced serum concentrations with most samples having levels below the lower limit of quantitation with increase in number of refills. The low systemic exposure may have precluded identification of systemic toxicities. This limitation is not considered to impact adequate safety assessment in this case, based on the comparative PK study showing serum concentrations after RPDS implant lower or within the range observed with 0.5 mg IVT Lucentis®. In addition, systemic ranibizumab concentrations in patients treated with RPDS 100 mg/mL were lower than that achieved in monkeys following IVT ranibizumab injections every other week (BLA 125156). Systemic exposure in monkeys is 3600X (C_{max}) and 2008X (AUC) greater than the exposure in patients treated with RPDS 100 mg/mL Q24W (see Systemic Exposure Margins section below). The Applicant also stated (Module 2.6.6 Toxicology Written Summary, page 26) that systemic ranibizumab concentrations in patients following treatment with RPDS 100 mg/mL are within the range experienced with monthly IVT ranibizumab 0.5 mg.

Systemic Exposure Margins:

Systemic exposure margins were calculated by the Applicant as the ratios of the observed exposures in the chronic IVT injection toxicology study (Study 01-463-1757; reviewed under BLA 125156) in which cynomolgus monkeys received ranibizumab 2 mg IVT every 2 weeks for 26 weeks (systemic NOAEL), relative to the exposure in humans with RPDS 100 mg/mL refilled Q24W. Safety factors were based on IVT injection dosing of ranibizumab in cynomolgus monkey because higher ocular and systemic exposures to ranibizumab were maintained compared with PDS studies in minipig.

Systemic safety factors ranged from 1500X, based on C_{max}, to 2100X, based on $AUC_{\tau,SS}$, see Applicant Table 4, Module 2.6.4 Pharmacokinetics Written Summary, page 16, copied below. The magnitude of the exposure margins support lack of concern for systemic toxicities.

Table 4 Systemic Exposure Margins Based on Exposures from the Nonclinical Intravitreal Injection Toxicology Study Compared with Exposures for the PDS Implant

Regimen	Route, Amount (Frequency)	Exposures		Safety Factors	
		C_{max} (ng/mL)	$AUC_{\tau,SS}$ (ng • day/mL)	Based on C_{max}	Based on $AUC_{\tau,SS}$
PDS in humans	Implant, 2.0 mg (Q24W refill-exchange) [a]	1.1 [b]	53.0 [c]	1500	2100
Observed Cynomolgus Monkey Chronic Toxicity Study	Intravitreal, 0.5, 1, 2 mg (Q14D) [d]	1,660	113,000	--	---

$AUC_{\tau,SS}$ = area under the concentration-time curve over the dosing interval at steady state; C_{max} = maximum concentration observed; CSR = clinical study report; PDS = Port Delivery System with ranibizumab; PK = pharmacokinetic; Q14D = once every 14 days; Q24W = once every 24 weeks.

[a] Refill amount is 20 µL of 100 mg/mL.

[b] C_{max} in humans used for the exposure margins is based on observed serum C_{max} (geometric mean) in patients treated with PDS 100 mg/mL in Phase II Study GX28228 (Ladder). Of the PDS clinical studies, Study GX28228 had the most frequent serum PK sampling approach. See Final CSR GX28228.

[c] Observed $AUC_{0\text{-}168d}$ in humans from PDS 100 mg/mL arm in Study GR40548. See Section 2.7.2, Summary of Clinical Pharmacology Studies for additional details.

[d] Dosage: 0.5 mg on Day 1, 1 mg on Day 15, and 2 mg on Day 29 and every 14 days subsequently (Study 01-463-1757). $AUC_{\tau,SS}$ corresponds to the reported $AUC_{d168\text{-}182}$, i.e., for the last dosing cycle, multiplied by 12 to reflect the 24-week dosing period in humans.

This reviewer finds this approach acceptable given the limitations to TK data collection observed in the minipig 6-month ocular toxicity study (i.e., exposure below lower limit of quantitation in most serum samples, data confounded by the presence of ATAs). However, this reviewer has the following observations:

- The Applicant used the highest human C_{max} (1.1 ng/mL) in Phase 2 Study # GX28228. The dosing regimen in this study (PRN) is not the intended dosing regimen (every 6 months). This reviewer believes the C_{max} observed in the pivotal Phase 3 Study GR40548 (using the intended dosing regimen) should be used.
    - The C_{max} values in Phase 3 Study GR40548 are 0.48 ng/mL (arithmetic mean) and 0.45 ng/ml (geometric mean). See Table 4, page 24, Module 2.7.2 Summary of Clinical Pharmacology Studies.
    - Exposure margin is therefore, 3458X, based on arithmetic mean.
    - Based on the magnitude of the exposure margins of 1500X or 3458X, the difference has no impact in safety assessment.
- The use of the AUC observed in Phase 3 Study GR40548 is acceptable as this is the clinical study that evaluated the intended dosing regimen. However, the value in the Applicant Table seems to be incorrect. The correct arithmetic mean is 59.48 ng•day/mL and the geometric mean is 56.27 ng•day/mL, per Table 4, Module 2.7.2 Summary of Clinical Pharmacology Studies, page 24.
    - Exposure margin is therefore, 1900X, based on arithmetic mean.

- Based on the magnitude of the exposure margins of 2100X or 1900X, the difference has no impact in safety assessment.

Ocular Exposure Margins:

As noted above, 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. Immunogenicity in animals may or may not be predictive of a similar effect in humans. Per summary information in the Toxicology Written Summary (Module 2.6.6, page 6 and 25), no safety signal relating to intraocular inflammation has been seen to date with the pivotal clinical RPDS data. The evaluated RPDS dose of 2.1 mg in the minipig (0.7 mg/mL vitreous) provides a 1.4X exposure margin for the 2.0 mg intended human dose (0.5 mg/eye), 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 C_{max} range observed with IVT injection.

The Applicant provided calculations of safety factors for ocular exposure of RPDS 100 mg/mL Q24W based on the predicted steady-state vitreous C_{max} and $AUC_{\tau,SS}$ values in cynomolgus monkey using the one-compartment model described in Study # 01-463-1757, which were 793 µg/mL and 28,600 µg•day/mL, respectively. The human vitreal C_{max} and $AUC_{\tau,SS}$ based on population PK analysis are predicted to be 25 µg/mL and 2,824 µg•day/mL, respectively, based on RPDS 100 mg/mL Q24W. Using this approach, the

estimated ocular safety factors are approximately 32-fold based on C_{max}, and 10-fold based on $AUC_{\tau,SS}$ (see Table 5, Module 2.6.4 Pharmacokinetics Written Summary, page 17).

Table 5 Ocular Exposure Margins Based on Predicted Vitreous Exposures for the Nonclinical Toxicology Study Compared with Predicted Vitreous Exposures for the PDS Implant

Simulated Regimen	Route, Amount (Frequency)	Exposures		Safety Factor	
		C_{max} (µg/mL)	$AUC_{\tau,SS}$ (µg • day/mL)	Based on C_{max}	Based on $AUC_{\tau,SS}$
PDS in humans	Implant, 2.0 mg Q24W refill-exchange [a]	25	2,824	32	10
Cynomolgus Monkey PK	2 mg ITV Q14D	793	28,600	—	—

$AUC_{\tau,SS}$ = area under the concentration-time curve over the dosing interval at steady state; C_{max} = maximum observed concentration; d = day; k_e = vitreal elimination rate; PDS = Port Delivery System with ranibizumab; PK = pharmacokinetic; Q14D = once every 14 days; Q24W = once every 24 weeks; $V_{vitreous}$ = vitreous volume of distribution.

Note: Cynomolgus monkey simulations were performed using a one-compartment model with $V_{vitreous}$ = 2.56 mL and k_e = 0.304 1/d, as described in Study 01-463-1757.

[a] Predicted vitreous exposures in humans are based on population PK analysis. See Section 2.7.2, Summary of Clinical Pharmacology Studies for additional details.

Modeled data, although supportive, is not generally used to make regulatory safety decisions. In addition, determination of the adequacy of the model to predict clinical PK data is outside Pharm/Tox purview.

In conclusion, the nonclinical studies conducted provide adequate safety support for use of the RPDS at the intended dosing regimen in the treatment of wet AMD. From the nonclinical perspective, approval is recommended.

The adequacy of the biocompatibility testing data to support the ocular safety of the implant is under the purview of CDRH review team.

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/s/

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