CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761197Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

BLA Number	761197
Link to EDR	docuBridge Link
Applicant	Genentech
Proposed Brand Name, Drug, Dosage Form and Strength	SUSVIMO, ranibizumab Injection, 100 mg/mL solution
Submission Type	Priority
Submission Date	4/23/2021
PUDFA Goal Date	10/23/2021
Proposed Indication	Treatment of patients with Neovascular (wet) Age-Related Macular Degeneration (AMD)
Proposed Dosing Regimen & Instructions	The proposed dose of SUSVIMO (ranibizumab) is 2 mg (0.02 mL of 10 mg/0.1 mL solution) continuously delivered via the permanent SUSVIMO implant with refills every 24 weeks (approximately 6 months)
Associated IND	113552
OCP Division	Division of Inflammation and Immune Pharmacology (DIIP)
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1. EXECUTIVE SUMMARY

The applicant has developed the Port Delivery System (PDS) with ranibizumab implant for the treatment of adult patients with Neovascular (wet) Age-Related Macular Degeneration (nAMD). Ranibizumab is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment binding to and inhibiting the biologic activity of human vascular endothelial growth factor A (VEGF-A). Ranibizumab injection, Lucentis®, was initially approved on June 30, 2006 for nAMD in BLA125156.

The proposed dosing regimen of PDS ranibizumab is 2 mg (0.02 mL of 100 mg/mL ranibizumab solution) continuously delivered via the the ocular PDS ranibizumab implant intravitreally (IVT) with refills every 24 weeks (approximately 6 months).

Clinical evidence supporting the efficacy, safety, and favorable benefit-risk assessment of PDS is based on the pivotal Phase 3 clinical study GR40548. Data from a dose-ranging Phase 2 Study GX28228 and the long-term extension Study GR40549 provided supporting evidence. The clinical pharmacology evaluations of PDS are based on serum and aqueous humor PK data obtained in Studies GX28228, GR40548, and GR40549.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the relevant Clinical Pharmacology information provided by the Applicant in BLA 761197 for PDS ranibizumab and recommends approval of this BLA. The key review issues with specific clinical pharmacology recommendations and comments are summarized below.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Pivotal study, GR40548, provides the evidence of effectiveness and safety of PDS ranibizumab. PDS ranibizumab 100 mg/mL Q24W achieved similar efficacy to monthly IVT ranibizumab 0.5 mg injections. Comparable systemic exposure and immunogenicity between the PDS ranibizumab 100 mg/mL Q24W and Q4W IVT injections of ranibizumab provide supporting evidence for efficacy and safety for PDS ranibizumab. Studies GX28228 and GR40549 provides supporting evidence.
General dosing instructions	The proposed PDS ranibizumab dosing of 2 mg (0.02 mL of 100 mg/mL solution) continuously delivered via the permanent PDS ranibizumab implant with refills administered every 24 weeks (approximately 6 months) is acceptable.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dosage adjustments in any patient subgroups (e.g., renal or hepatic impairment) are needed.

Labeling	The proposed Clinical Pharmacology relevant information in Section 6.2 is acceptable with minor edits. Regarding the information proposed in Section 12.3, the proposed information will be acceptable after agreement on several editis. The major edits are summarized as follows: 1. (b) (4) . 2. The PK information for the product label will primarily be derived from pivotal study, GX40548, (b) (4) . This issue was brought to the attention of the review team by the Clinical Pharmacology team during the time of Mid-Cycle Meeting for this BLA and the recommendation from the clinical team was (b) (4) . In addition, the clinical team stated that even higher concentrations of ranibizumab were possibly observed during product development of original BLA125156 (Lucentis) leading to much higher Cmax and no systemic safety concern was identified. Furthermore, it was stated that there appears to be no significantly different systemic safety concerns with the proposed PDS product in the development program compared to 0.5 mg IVT ranibizumab Q4W. Note that the (b) (4) is also unlikely to have any meaningful impact on the pharmacometrics review conclusions as confirmed by the pharmacometrics reviewer in Section 4.2.3 of this review. Study GX40548 assesses the PK and immunogenicity for the final TBM product at the final dosing regimen of Q24W and is deemed to be sufficient to describe the PK of PDS ranibizumab. The PK results from GR40548 appear to be in alignment with the PK results for Q24W regimen from available PK results from Study GR40549. There may be other edits provided to the USPI that are not captured here but will be finalized as the labeling discussions are held internally and with the applicant regarding this BLA.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulation was used in the pivotal clinical study.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Ranibizumab is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment binding to and inhibiting the biologic activity of human vascular endothelial growth factor A (VEGF-A).

The applicant has developed PDS ranibizumab ocular implant for the treatment of adult patients with nAMD. The clinical pharmacology evaluations of PDS are based on serum and aqueous humor PK data obtained in Studies GX28228, GR40548, and GR40549. The PK study results summary from Studies GX28228 and GR40549 can be seen in Appendix Section 4.3 of this review. The information on the systemic PK exposure to the TBM PDS ranibizumab 100 mg/mL is primarily informed by results from pivotal clinical study GR40548 for the reasons stated in Section 1.1 of this review:

Pharmacokinetics
Following administration of PDS ranibizumab 100 mg/mL, the ranibizumab mean (SD) maximum serum concentration was 0.48±0.17 ng/mL and median time to maximum serum concentration was 26.06 Days.

Refer to Section 3.2 for details on clinical pharmacology assessment.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed dose of PDS ranibizumab is 2 mg (0.02 mL of 100 mg/mL solution) continuously delivered via the permanent PDS ranibizumab implant with refills administered every 24 weeks (approximately 6 months). This dosing regimen was evaluated in the pivotal clinical trial (Study GR40548) in patients with nAMD.

2.2.2 Therapeutic individualization

No dose adjustment is necessary for any specific populations.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

Labeling recommendations are summarized in Section 1.1 of the review.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

The PDS with ranibizumab is an intraocular drug delivery system that consists of an ocular implant, a customized formulation of ranibizumab (100 mg/mL), and 4 ancillary devices used to fill, insert, refill-exchange, and explant the implant. PDS is designed to continuously release the customized formulation of ranibizumab into the eye over time. The PDS implant can be refilled via a refill-exchange procedure, during which the contents of the implant are exchanged with fresh ranibizumab after extended

intervals. The proposed PDS ranibizumab dosing in this BLA is 2 mg (0.02 mL of 100 mg/mL solution) continuously delivered via the permanent PDS ranibizumab implant with refills administered every 24 weeks (approximately 6 months). Ranibizumab injection, Lucentis®, was initially approved on June 30, 2006 for nAMD in BLA125156.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Ranibizumab is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment binding to and inhibiting the biologic activity of human vascular endothelial growth factor A (VEGF-A).

The relevant systemic PK and immunogenicity findings for PDS ranibizumab are summarized below:

Absorption/Distribution:
The PK parameters from Study GR40548 are summarized in Table 1. The PK relevant aspects of the study design are discussed in Appendix Section 4.4 of this review. Following administration of PDS ranibizumab 100 mg/mL, the ranibizumab mean±SD maximum serum concentration was 0.48±0.17 ng/mL and median time to maximum serum concentration was 26.06 Days.

Table 1. 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: Table 4 from Module 2.7.2 of BLA 761197

The ranibizumab PK in aqueous humor are generally consistent with the PK in serum. In both the PDS 100 mg/mL arm and IVT arm, the aqueous humor and serum PK are consistent with flip-flop kinetics, with serum ranibizumab concentrations approximately 3000-9000 fold lower than aqueous humor concentrations (Table 2).

Table 2. Summary of Ranibizumab Concentrations by Matrix and Treatment, Study GR40548

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

PDS = Port Delivery System with ranibizumab; Q24W = every 24 weeks; Q4W = every 4 weeks
N = numbers of treated patients; n = numbers of aqueous humor or serum samples at a given timepoint

Source: Table 5 from Module 2.7.2 of BLA 761197

Elimination:

Metabolism: Ranibizumab is a monoclonal antibody fragment and antibodies are cleared principally by catabolism.

Vitreal and serum pharmacokinetics following treatment with PDS ranibizumab exhibit rate-limited elimination, driven by the release of ranibizumab from the PDS ranibinumab implant.

Excretion: The serum half-life of ranibizmab from PDS ranibizumab should be interpreted with caution due to the estimation of half-life from a limited number of patients (n = 5).

Immunogenicity:

Overall, the incidence of treatment-emergent anti-drug antibody (ADA) and neutralizing antibody (NAb) to ranibizumab administered via the PDS in Studies GX28228 and GR40548 were low, and in a similar range as previously observed (2.0-9.4%) for IVT ranibizumab clinical studies. The details of the immunogenicity results from Study GR40548 can be seen in Appendix Section 4.5 of the review. Exploratory analyses in Study GR40548 indicated that the occurrence of ADAs (including NAbs) to ranibizumab did not appear to result in any clinically meaningful consequences with respect to PK, efficacy or safety. However, due to the low incidence of ADAs observed to date, the results do not provide definitive conclusions. See Section 3.3.4 for additional details. In consideration of these findings and the comparable AE profiles between ADA-positive and ADA-negative patients, no clear impact to treatment efficacy or safety was observed in ADA-positive patients. In conclusion, ranibizumab immunogenicity has been assessed following two routes of ocular administration: IVT injection and via the PDS. No clinically meaningful difference in the immunogenicity risk between these two routes of administration has been observed.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The efficacy and safety of the proposed PDS ranibizumab dosing regimen in patients with nAMD was evaluated primarily in pivotal study GR40548 and and supportive evidence is derived from Studies GX28228 and GR40549. Comparable systemic exposure and immunogenicity between the PDS ranibizumab 100 mg/mL Q24W and Q4W IVT injections of ranibizumab provide supporting evidence for efficacy and safety for PDS ranibizumab. For additional information, see Sections 3.3.2, 3.3.3, and 3.3.4 of this review.

See clinical review for additional details regarding evidence of effectiveness and safety for the proposed product.

Since PDS ranibizumab is administered via IVT route and the site of action is eye, the systematic exposure is not expected to affect treatment effect by mechanism. Therefore, the exposure-efficacy relationship was not evaluated.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen is appropriate for the patient population for which the indication is being sought. The recommended dosing regimen is a PDS initial implant fill with 0.02 mL of ranibizumab 100 mg/mL, followed by subsequent refill-exchanges with 0.02 mL of 100 mg/mL Q24W. The recommended dosing regimen is supported by the following:

Based on the clinical safety and efficacy data from the dose-ranging study GX28228, it appears that ranibizumab concentrations of 10 and 40 mg/mL in the PDS with pro re nata (PRN) refill-exchanges were observed to be less effective than 100 mg/mL ranibizmab. In Study GX28228, at Month 6, 62%, 70%, and 80% of patients did not require a refill per protocol-defined criteria for the PDS 10 mg/mL, 40 mg/mL, and 100 mg/mL arms, respectively. The mean BCVA changes from baseline at Month 9, based on observed data were +3.3 letters in the IVT arm and -3.1, +0.2, and +4.8 letters in the PDS 10 mg/mL, 40 mg/mL, and 100 mg/mL arms, respectively, which support a dose response. The mean BCVA change in the PDS 100 mg/mL was similar to that in IVT arm after Month 4, with a mean difference at Month 9 of +1.6 letters (95% CI: -1.8, +4.9). For additional details on efficacy aspects with the proposed dosing regimen, see Clinical review. Considering above observation in dose ranging study, dose of 0.02 mL of 100 mg/ml PDS ranibizumab was selected for pivotal Phase 3 study GR40548. An overview of clinical studies is presented in Table 3.

Table 3. Overview of Clinical Studies

Study No.	Study Design, Control Type	Dose, Route, and Regimen	Patient Population	No. of Patients
GX28228 (Ladder main study) Supportive Study	Phase II, Multicenter, dose-ranging, randomized, active treatment (monthly intravitreal injection)–controlled study (complete)	PDS 10 mg/mL, PRN PDS 40 mg/mL, PRN PDS 100 mg/mL, PRN Intravitreal ranibizumab injection (0.5 mg) monthly	Patients with nAMD responsive to anti VEGF with maximum 9 months since diagnosis; BCVA 20/20 to 20/200; subfoveal CNV or juxtafoveal with subfoveal component	232 patients randomized [a] -PDS 10 mg/mL PRN arm: 58 patients -PDS 40 mg/mL PRN arm: 62 patients -PDS 100 mg/mL PRN arm: 59 patients -Intravitreal ranibizumab injection (0.5 mg) monthly arm: 41 patients
GX28228 (Ladder) Oral Antithrombotic Substudy	Non-randomized, uncontrolled, open-label substudy	PDS 100 mg/mL, refill-exchanged PRN up to maximum of 6 months between refill-exchanges	Patients with nAMD treated with prior anti-VEGF intravitreal injections, who require ongoing oral antithrombotic therapy	12 enrolled 11 PDS 1 patient not treated
GR40548 (Archway) pivotal study	Phase III, Randomized, multicenter, open-label (VA–masked), active-comparator study (ongoing)	PDS 100 mg/mL Q24W Intravitreal ranibizumab injection (0.5 mg) Q4W	Patients with nAMD responsive to anti VEGF treatment with maximum 9 months since diagnosis; BCVA 20/200 or better; any type of macular CNV	418 patients randomized [b] -PDS 100 mg/mL Q24W: 248 patients -Intravitreal ranibizumab injection (0.5 mg) Q4W: 167 patients - 3 patients not treated
Study No.	**Study Design, Control Type**	**Dose, Route, and Regimen**	**Patient Population**	**No. of Patients**
GR40549[c] (Portal) extension study	Phase III, Multicenter, open-label, visual assessor–masked, multiple-cohort extension study (ongoing)	PDS 100 mg/mL Q24W	Patients with nAMD who have completed either Phase II Study GX28228 (Ladder) or Phase III Study GR40548 (Archway)	220 patients enrolled [b, d] -PDS 100 mg/mL Q24W: 217 patients -13 patients from Study GR40548 -189 patients from Study GX28228 main study -11 patients from oral antithrombotic substudy of GX28228

BCVA = best corrected visual acuity; CNV = choroidal neovascularization; nAMD = neovascular age-related macular degeneration; PDS = Port Delivery System with ranibizumab; PRN = pro re nata; Q4W = every 4 weeks; Q24W = every 24 weeks; VA = visual assessor; VEGF = vascular endothelial growth factor.

[a] Five patients randomized to the PDS groups decided not to undergo implantation because of the unexpectedly high incidence of vitreous hemorrhage before optimization of the Instructions for Use. Seven patients from a non-compliant site were randomized and treated but were not analyzed.

[b] As of clinical cutoff date 11 September 2020.

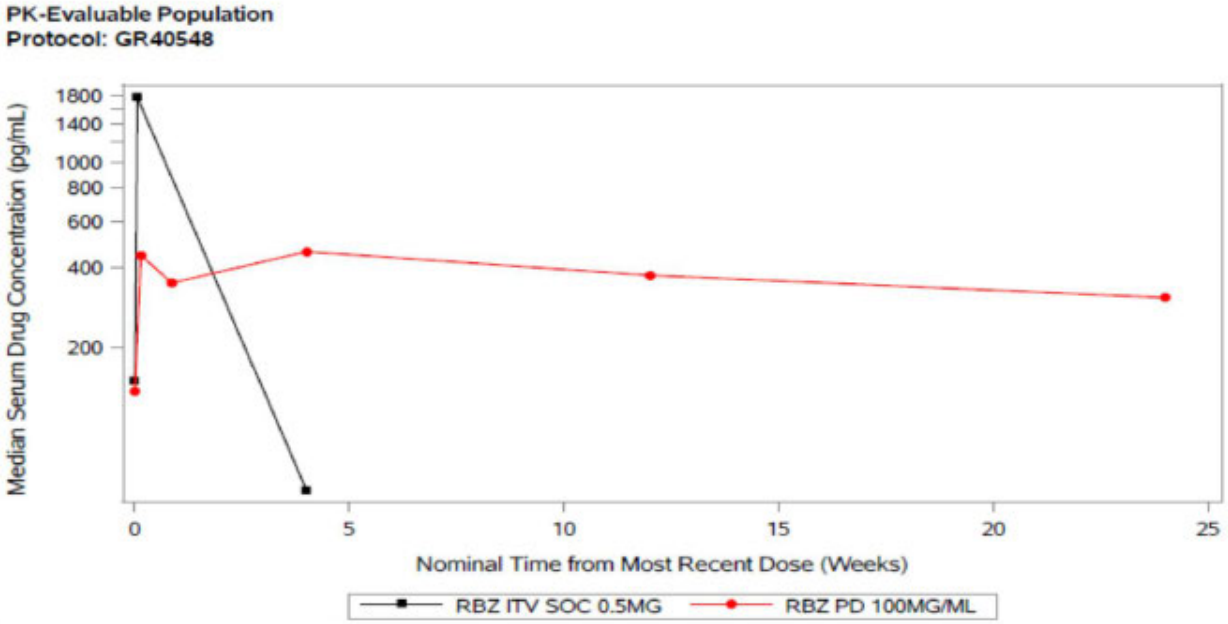
[c] Immunogenicity was not assessed in Study GR40549.

[d] Three patients enrolled in the PDS 100 mg/mL arm were not treated. Four patients from the non-compliant Study GX28228 site were not included in the analyses.

Source: Table 1 of Module 2.7.2 from BLA 761197

PK data (Figure 1) from the pivotal study GR40548 and population-PK analysis (Table 9 and Figure 5 of in Appendix Section 4.2) of this review demonstrated that ranibizumab ocular and systemic concentrations following treatment with PDS 100 mg/mL Q24W were within the range (Cmax - Cmin) of concentrations experienced with monthly IVT ranibizumab 0.5 mg injections. In the PK-Evaluable Population in the IVT arm, the geometric mean serum ranibizumab concentration was 1840 pg/mL from sampling near Cmax (1 – 5 days after injection) and ranged from 28.8 – 58.9 pg/mL at 4 weeks (Cmin) after IVT injection across the timepoints evaluated through Week 72. In the PK-Evaluable Population for the patients from selected study sites with additional PK sampling in the PDS 100 mg/mL arm, the observed geometric mean Cmax and Cmin were 450 pg/mL and 300 pg/mL, respectively. The serum ranibizumab concentration-time profile in the PDS 100 mg/mL arm was consistent across implantation and subsequent refill-exchanges; 4 weeks post refill-exchange ranged from 479-558 pg/mL at Weeks 28 and 52, and 24 weeks post-refill-exchange ranged from 210-250 pg/mL at Weeks 48 and 72.

Figure 1. Plot of Log-Scale Median Serum Ranibizumab Concentrations from Most Recent Dose Time by Treatment for PK-Evaluable Population, Study GR40548



ITV = intravitreal; PDS = Port Delivery System with ranibizumab; PK = pharmacokinetic; RBZ = ranibizumab

Note: Timepoints with at least 5 subjects are included in this plot. ITVPKO samples collected at 1-5 days postdose in the intravitreal arm was assigned as 3 days (or 0.4 weeks) postdose.

RBZ PD 100MG/ML is the same as PDS 100 mg/mL

ITV = IVT

Source: Adapted from Figure 4 of Module 2.7.2 from BLA 761197

Since PDS ranibizumab is administered via IVT route and the site of action is eye, the systematic exposure is not expected to affect treatment effect by mechanism. Therefore, the exposure-efficacy relationship was not evaluated.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

An alternate dosing regimen is not needed for any of the subpopulations. For the proposed drug product, the intended site of drug delivery and action is the eye; therefore, the extent of systemic exposure based on differences among subpopulations is not likely to influence the proposed drug product's efficacy. The Applicant assessed the impact of renal impairment on the PK of ranibizumab upon administration of PDS ranibizumab. As the drug's site of action is eye and the majority of patients (75%) tested in the clinical trials have renal impairment, the increase in systemic exposure in patients with renal impairment is not considered clinically significant. Thus, no dose adjustment is needed in patients with renal impairment.

3.3.4 What is the impact of immunogenicity on exposure, safety and efficacy of PDS ranibizumab?

Assessment

In Study GR40548, ADAs and NAbs were assessed at randomization (pre-dose), Month 1 (Week 4), Month 6 (Week 24), Month 9 (Week 36), final study visit (Week 96), and/or at early study termination visit.

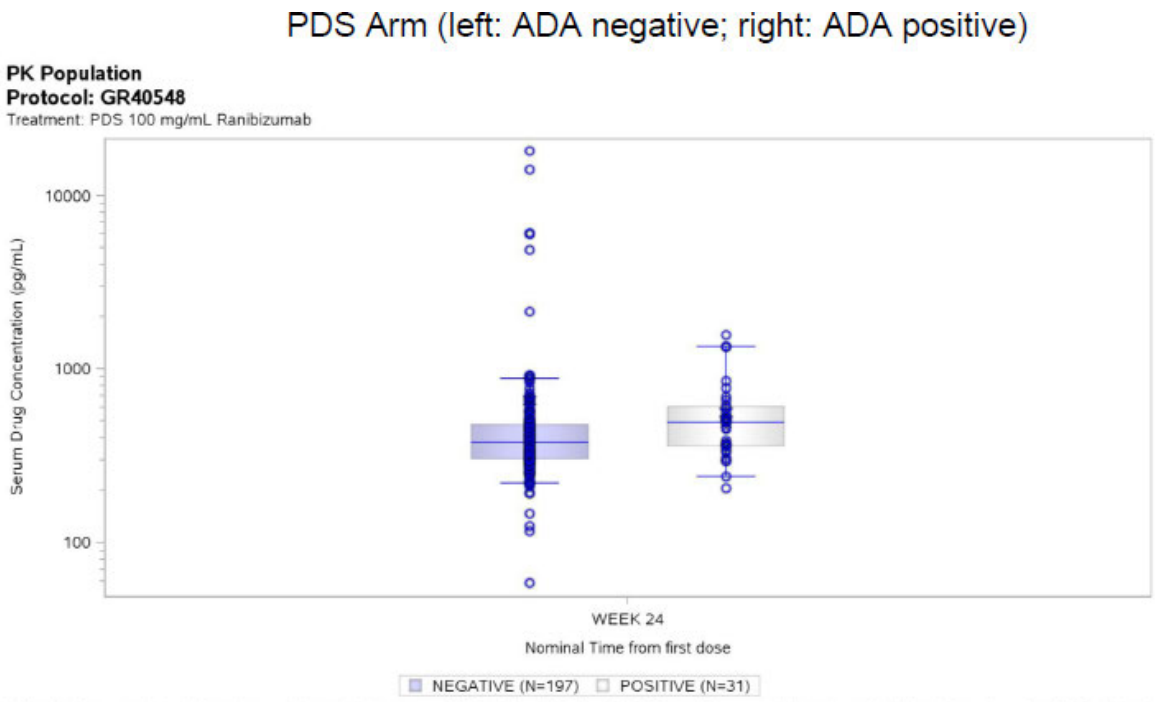
Incidence

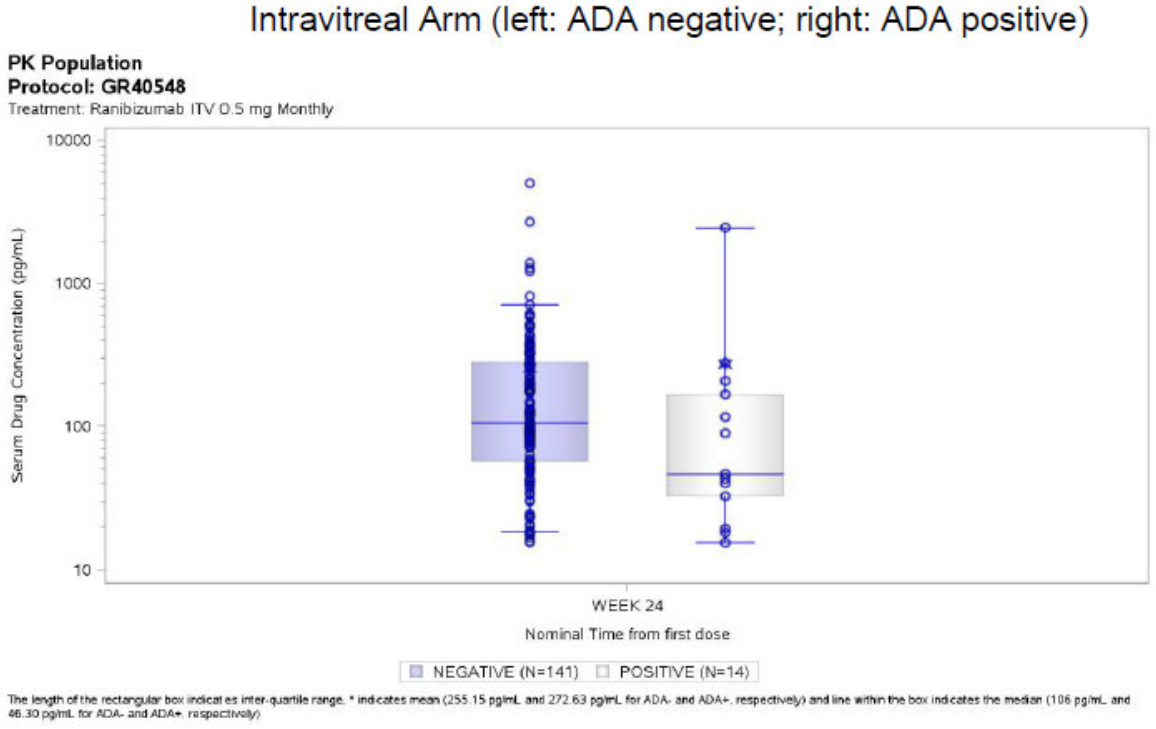
In Study GR40548, the baseline prevalence of anti-ranibizumab ADAs was 5 of 243 patients (2.1%) in the PDS 100 mg/mL arm and in 8 of 162 patients (4.9%) in the IVT arm. The overall incidence of treatment-emergent anti-ranibizumab ADA was 29 of 247 patients (11.7%) in the PDS 100 mg/mL arm and in 10 of 165 patients (6.1%) in the IVT arm. The overall baseline prevalence of NAb to ranibizumab was low with 1 of 243 (0.4%), and 2 of 162 (1.2%) baseline-evaluable patients in the PDS 100 mg/mL arm and IVT arm, respectively. Incidence of treatment-emergent NAb to ranibizumab was also low with 13 of 247 patients (5.3%) and 4 of 165 patients (2.4%) testing positive in the PDS 100 mg/mL arm and IVT arm, respectively. For additional details on immunogenicity results for PDS ranibzumab compared to IVT ranibizumab, see Appendix Section 4.5 of the review.

Impact of ADA on PK

ADA impact on ranibizumab serum concentrations was evaluated in the PK population based on serum ranibizumab concentrations at Week 24 (representing a trough sample in both PDS and IVT arms). No apparent impact of ADA status on serum PK was observed in either treatment arm as seen in Figure 2.

Figure 2. Plot of Serum Ranibizumab Concentrations at Week 24 by Treatment and ADA Status





Source: Figure 2 of Integrated Summary of Immunogenicity Report from BLA 761197

Impact of ADA on Efficacy

Given the low number of patients with a positive ADA or NAb response to ranibizumab in Study GR40548, it is not possible to make definite conclusions on the impact of ADAs or NAbs on efficacy; however, there did not appear to be a meaningful difference in change from baseline in BCVA in the study eye at Week 40, between ADA-positive and ADA-negative, or between NAb-positive patients and NAb-negative patients (Table 4).

Table 4. Summary of Change from baseline in BCVA at Week 40 by ADA and NaB Status

Study GR40548 (CCOD: 27March2020)		
	PDS 100 mg/mL Arm (N = 247)	Intravitreal Arm (N = 167)
ADA Negative, n	213	149
Change from baseline in BCVA at Week 40		
Mean (SD)	0.2 (9.05)	0.4 (7.34)
95% CI	(-1.0, 1.5)	(-0.8, 1.6)
ADA Positive, n	34	15
Change from baseline in BCVA at Week 40		
Mean (SD)	0.0 (7.86)	2.9 (4.45)
95% CI	(-2.8, 2.8)	(0.4, 5.5)
NAb Negative, n	18	7
Change from baseline in BCVA at Week 40		
Mean (SD)	0.5 (7.00)	4.1 (4.26)
95% CI	(-3.0, 4.0)	(0.2, 8.1)
NAb Positive, n	14	7
Change from baseline in BCVA at Week 40		
Mean (SD)	-1.2 (9.36)	1.8 (5.04)
95% CI	(-6.9, 4.4)	(-3.5, 7.1)

ADA = anti-drug antibody; BCVA = best corrected visual acuity letter score; CCOD = clinical cut-off date; NAb = Neutralizing antibody; PDS = Port Delivery System with ranibizumab; SD = standard deviation.

Source: Table 8 of Integrated Summary of Immunogenicity Report from BLA 761197

Impact of ADA on Safety

There were no major differences in the ocular or non-ocular adverse event (AE) profiles between ADA-positive patients in PDS 100 mg/mL arm and ADA-positive patients in IVT arm. As immunogenicity to IVT administered recombinant therapeutics may result in development of intraocular inflammation, summaries of intraocular inflammation by ADA and NAb status were performed and can be seen in Table 5. Overall, the safety profile related to ranibizumab observed in

Study GR40548 is consistent with known experience with IVT administration of ranibizumab in previous clinical trials. In consideration of this and the comparable AE profiles between ADA-positive and ADA-negative patients in Study GR40548, no clear impact to safety was observed in patients with ADA positivity.

Table 5. Summary of Intraocular Inflammation in Study Eye by ADA and NAb Status

Study GR40548 (CCOD: 11 Sept 2020)				
	PDS 100 mg/mL Arm (N = 247)		Intravitreal Arm (N = 165)	
	Through 37 days	Day 38 to Day 294	Through 37 days	Day 38 to Day 294
ADA Negative				
# of Patients with intraocular inflammation/ADA Negative patients (%)	49/213 (23.0%)	12/213 (5.6%)	1/149 (0.7%)	0
ADA Positive				
# of Patients with intraocular inflammation/ADA Positive patients (%)	8/34 (23.5%)	1/34 (2.9%)	0	0
NAb Negative				
# of Patients with intraocular inflammation/NAb Negative patients (%)	4/18 (22.2%)	1/18 (5.6%)	0	0
NAb Positive				
# of Patients with intraocular inflammation/NAb Positive patients (%)	3/14 (21.4%)	0	0	0

ADA = anti-drug antibody; CCOD = clinical cut-off date; NAb = Neutralizing antibody; PDS = Port Delivery System with ranibizumab.

Source: Table 9 of Integrated Summary of Immunogenicity Report from BLA 761197

3.3.5 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

The drug product is given via IVT route; therefore, the issue of a food-drug interaction is not relevant.

No drug interaction studies were conducted in vitro or in vivo. However, drug-drug interactions are not expected based on CYP450, other metabolizing enzymes, or transporters, since ranibizumab metabolism does not utilize these pathways.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Ranibizumab concentrations in human serum were measured using a validated enzyme-linked immunosorbent assay (ELISA) method with a lower limit of quantitation (LLOQ) of 15.0 pg/mL to 600 pg/mL upper limit of quantification (ULOQ). The analytical method validation and performance were deemed acceptable.

The sample preparation, stability, analysis accuracy, and precision in relevant clinical pharmacology studies were reviewed by the Clinical Pharmacology reviewer and are deemed acceptable. A summary of the validation parameters for the ELISA method can be seen in Table 6.

Table 6. Summary of Validated ELISA Method Used to Measure Ranibizumab in Serum

Assay	ELISA for the determination of ranibizumab concentration in Human Serum
Validation Report No.	VHR-Human-PK-MARA
Biological Matrix	Human serum
Validation and Sample Analysis Site	(b) (4)
Internal Standard	ranibizumab
Minimum Required Dilution	1:2
LLOQ	15.0 pg/mL
Validated Assay Range	15.0 pg/mL to 600 pg/mL
Regression Model and Weight	4-parameter algorithm (regression method "Z" in Assist)
Control Concentrations	30.0, 100 and 400 pg/mL
Accuracy Range (% Difference)	-6.19% to -1.26%
Inter-Assay Precision Range (%CV)	4.99% to 8.77%
Intra-Assay Precision Range (%CV)	1.65% to 9.20%
Dilutional Linearity	Samples can be diluted up to 1:1500
Interference	**Non-interfering and not cross-reactive**: Human whole blood (up to 10%) Lipids (up to 400 pg/mL) rhVEGF (up to 10 ng/mL) rhVEGF R1 (up to 1,000 ng/mL) **Cross-reactive and non-interfering**: rhVEGF (at 100 ng/mL) **Interfering and cross-reactive**: Bevacizumab (100 pg/mL)
Selectivity	Acceptable in human serum from patients with AMD
Studies	FH-1.2, GX28228, GR40548, GR40549

AMD=Age-related macular degeneration; CV=coefficient of variation; LLOQ=lower limit of quantification

Source: Table 3 of Module 2.7.1 from BLA 761197

ADA, NAb in human serum: Refer to the CMC/OBP immunogenicity review for further details on the adequacy of the assays.

4.2 Population PK Analyses

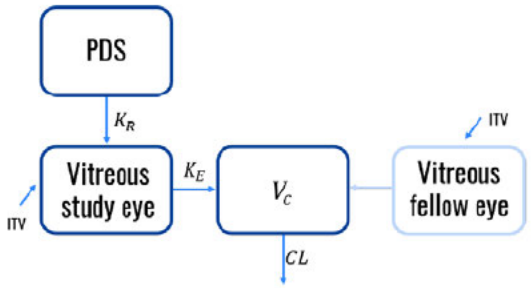
4.2.1 Executive Summary

PopPK modeling is adequate to characterize the PK profile of ranibizumab in serum.

Creatinine clearance is a significant covariate on clearance. Patients with renal impairment have lower clearance and higher exposure compared to patients with normal renal function. As drug's site of action is eye and the majority of patients (75%) tested in the clinical trial have renal impairment, the increase in systemic exposure in patients with renal impairment is not considered clinically significant.

Because of the limited number of samples and lack of time-series data, no robust assessment of predicted versus observed vitreous concentrations from IVT and PDS delivery system can be made.

4.2.2 PPK Assessment Summary

Goal of PPK analysis		• Characterize ranibizumab's PK profile in serum and predict ranibizumab concentrations in the vitreous • Explore the source of ranibizumab PK variability to identify need for individualized dosing	
Study included		Phase 2 study GX28228 (Ladder)	
Population included		Patients with neovascular age-related macular degeneration (nAMD) (N=164)	
Population characteristics	General	76 yrs (50-92); 78.2 kg (34.2-169); 58 (35.4%) males;	
	Organ impairment	RI: 41 (25%) normal, 75 (45.7%) mild, 42 (25.6%) moderate, 4 (3.7%) severe	
Dose(s) included in PPK		PDS: 10 mg/mL, 40 mg/mL, 100 mg/mL; IVT injection	
No. of patients, PK samples, and BLQ		164 patients, 3534 PK samples in final PK model. 532 LLOQ PK excluded.	
Model structure		A one-compartment disposition model with two vitreous compartments linked to the serum, one for study eye and one for fellow eye. A PDS compartment was linked to the vitreous compartment of the study eye. 	
Covariates evaluated		Creatinine clearance (CRCL) on clearance (CL), as well as age and gender on device release rate (k_R)	
Model		**Summary**	**Acceptability**
Population characteristics		*Table 7*	N/A

Uncertainty and variability (RSE, IIV, bootstrap, shrinkage)	The magnitude of the IIV was mild for CL (25.6% CV). The shrinkage for IIV of CL is also small (13.3%) (Table 8).	Yes
BLQ for parameter accuracy	532 out of 4069 PK samples below LLOQ were excluded.	PK samples below LLOQ excluded from the popPK analysis accounts for about 10% of total observations.
GOF, VPC 	No signs of model misspecification were identified in the goodness-of-fit plots (**Figure 4**). Prediction-corrected visual predictive check showed that the final model adequately described the observed PK profile of ranibizumab across different PDS dosing regimens and IVT injection (Figure 5).	
Significant covariates and clinical relevance	Creatinine clearance is a significant covariate on clearance. Patients with renal impairment have lower clearance and higher exposure compared to patients with normal renal function (Figure 6). No clinically significant differences in the pharmacokinetics of ranibizumab were observed based on age	As drug's site of action is eye and the majority of patients (75%) tested in the clinical trial have renal impairment, the increase in systemic exposure in patients with renal impairment is not considered clinically significant. Thus, no dose adjustment is needed in patients with renal impairment.

PK Simulation	Predicted Serum Exposure for PDS 100 mg/mL and IVT 0.5 mg is provide in Table 9.	The VPC and model simulation showed that ranibizumab serum concentrations following treatment with PDS 100 mg/mL Q24W are within the range of concentrations experienced with monthly IVT ranibizumab 0.5 mg injections.
Labeling language	**Description**	**Acceptability/Action**
12.3 PK	(b) (4)	No, see review issue below

4.2.3 Population PK Review Issues

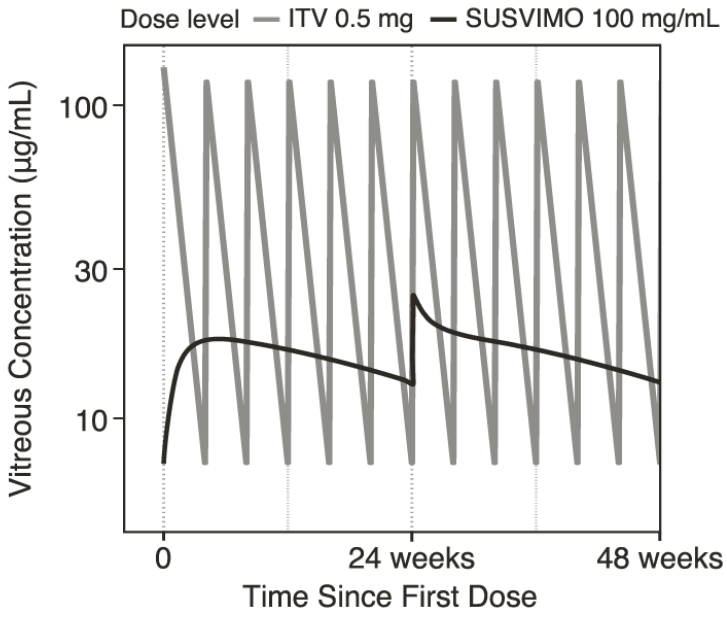
A figure illustrating predicted vitreous ranibizumab concentration versus time of SUSVIMO was provided by the applicant and (b) (4).

FDA recommends (b) (4). Only 5 of the patients included in the PopPK analysis had a vitreous observation, 3 received PDS 10 mg/mL and 2 received PDS 40 mg/mL. None of the vitreous samples were from the PDS 100 mg/mL dose. Based on the limited number of samples and lack of time-series data, no robust assessment of predicted versus observed vitreous concentrations from ITV 0.5 mg and PDS 100 mg/ml can be made. While such model prediction may help to characterize the concentration-time profile of IVT and PDS delivery system, robust assessment of prediction versus observation was not conducted. Therefore, FDA recommends (b) (4).

Based on popPK model prediction, serum ranibizumab exposure following SUSVIMO implant administration is predicted to be approximately 50,000-fold lower than vitreal ranibizumab exposure. This prediction is not confirmed with observed data, but it is consistent with the predicted 90,000-fold lower serum concentrations compared to vitreal concentrations following IVT injection.

(b) (4) is unlikely to have any meaningful impact on the pharmacometrics conclusions.

Figure 3. [redacted] (b) (4) **Predicted vitreous ranibizumab concentration versus time of SUSVIMO and monthly 0.5 mg intravitreal ranibizumab injection.**



Source: [redacted] (b) (4)

Table 7. Summary of Baseline Characteristics and Laboratory Values in the Dataset.

Parameter	PDS 10 mg/mL	PDS 40 mg/mL	PDS 100 mg/mL	Intravitreal injection 0.5 mg	All
	(N=42)	(N=49)	(N=41)	(N=32)	(N=164)
Age (yr)					
Mean (SD)	75 (8.7)	74.6 (8.9)	74.8 (8.3)	72.1 (8.6)	74.2 (8.6)
Median (range)	77 (56 - 92)	75 (50 - 90)	76 (57 - 91)	73 (52 - 85)	76 (50 - 92)
Weight (kg)					
Mean (SD)	78.9 (16)	79.6 (21)	81.2 (21)	78.2 (14)	79.5 (18)
Median (range)	75.8 (46 - 118)	78 (34.2 - 169)	78.7 (50.3 - 145)	78.9 (55.3 - 100)	78.2 (34.2 - 169)
Gender					
Female	25 (59.5%)	31 (63.3%)	28 (68.3%)	22 (68.8%)	106 (64.6%)
Male	17 (40.5%)	18 (36.7%)	13 (31.7%)	10 (31.2%)	58 (35.4%)
Creatinine Clearance (mL/min)					
Mean (SD)	74.6 (25)	75.8 (28)	73.3 (30)	76.3 (23)	75 (26)
Median (range)	71.1 (33.3 - 126)	73.9 (27.6 - 150)	72.7 (13.4 - 143)	75.8 (27.8 - 134)	73.2 (13.4 - 150)

Source: Table 3 in Applicant's population PK report

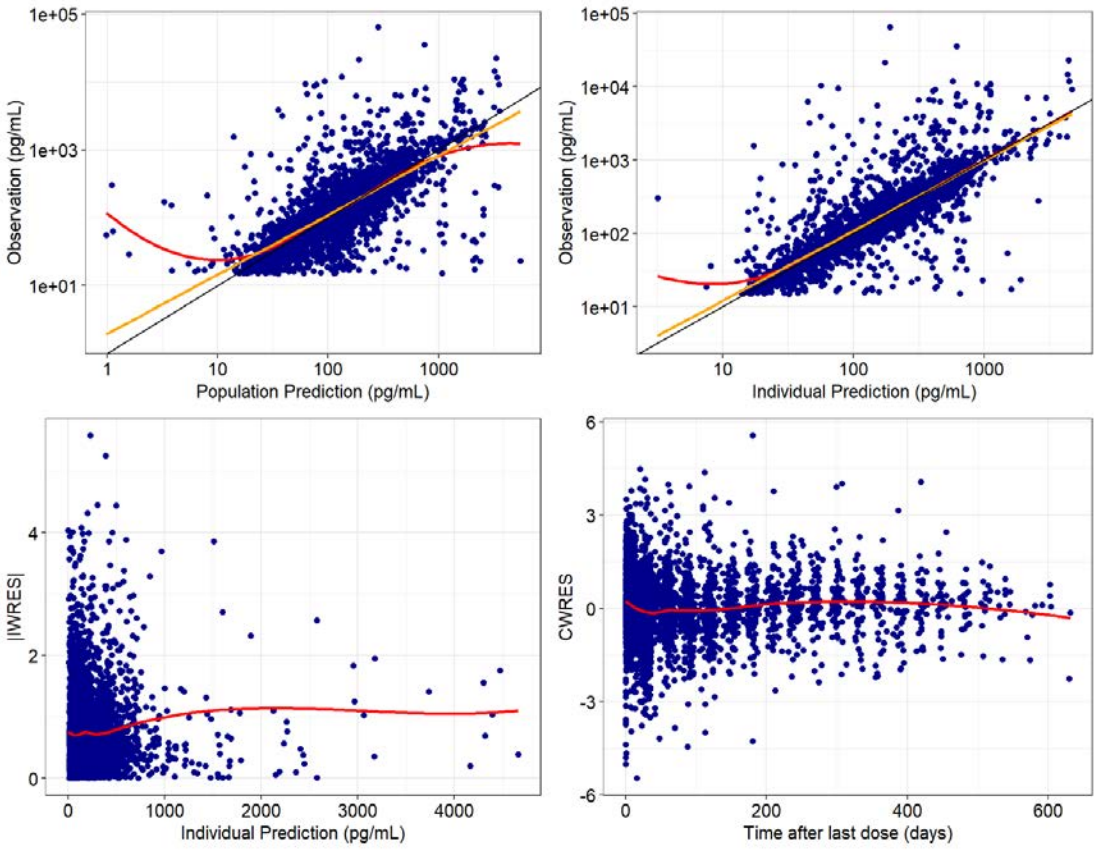
Table 8. Parameter Estimates of the Base and Final PopPK Model

Parameter	Label	Estimate	Unit	CI95
θ_2	CL	21800	mL/day	(20600 - 22900)
θ_4	k_r,0	0.00445	d^{-1}	(0.00418 - 0.00473)
θ_8	Time slope k_r	0.664	Proportion/year	(0.568 - 0.777)
θ_{10}	Concentration slope-k_r*	-0.00369	Proportion/(mg/μL)	(-0.00565 - -0.001705)
θ_9	CrCL-CL	0.639	-	(0.501 - 0.778)
θ_5	Early residual error	0.738	Proportion	(0.723 - 0.753)
θ_6	Residual error	0.285	Proportion	(0.278 - 0.291)
θ_7	Rate constant early error	0.208	d^{-1}	(0.199 - 0.216)
ω_1	IIV Residual Error	0.699	SD	(0.633 - 0.765)
ω_3	IIV CL	0.257	SD	(0.245 - 0.269)
ω_4	IIV k_r	0.162	SD	(0.151 - 0.173)
ω_{29}	IIV Time slope	0.414	SD	(0.253 - 0.575)

k_r: Device (implant) release rate. IIV: Inter-individual variability. CrCL: Creatinine clearance. CL: Systemic clearance. SD: Standard deviation, log-normally distributed.

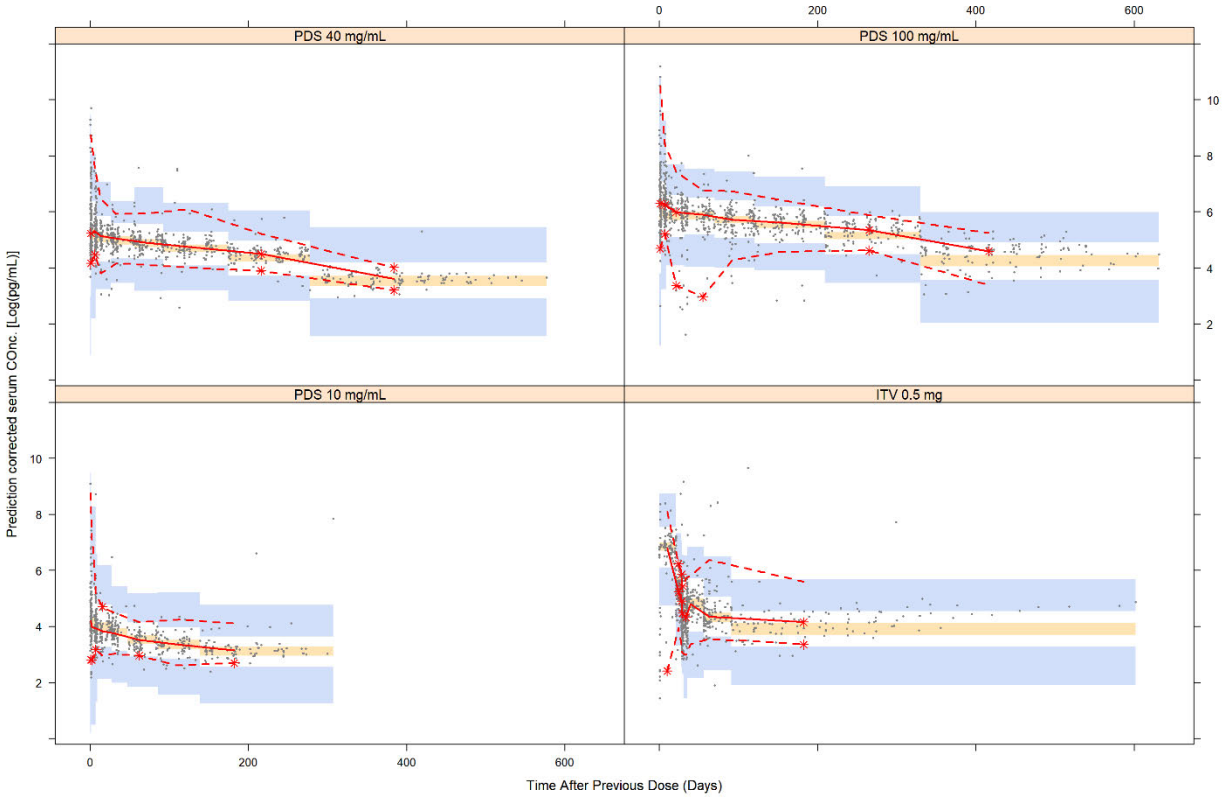
Source: Table S.1 in Applicant's population PK report

Figure 4: Goodness of Fit Plots of the Final Model



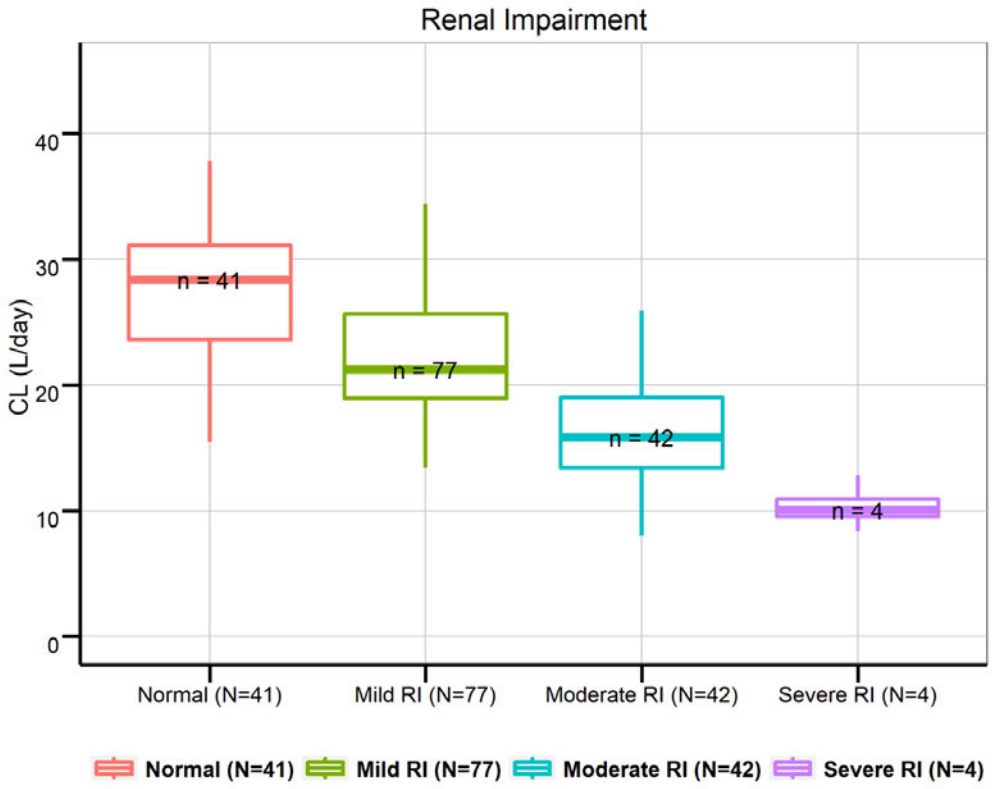
Source: Reviewer's Analysis based on dataset "poppk-06feb2020-qp-2020-02-28.csv"

Figure 5. Visual Predictive Checks of Ranibizumab Concentration-Time Data Stratified by Dosing Regimens.



Source: Reviewer's Analysis based on dataset "poppk-06feb2020-qp-2020-02-28.csv"

Figure 6. Distribution of Clearance across Patients with Different Renal Function.



Source: Reviewer's Analysis based on dataset "poppk-06feb2020-qp-2020-02-28.csv"

Table 9. Predicted Serum Exposure for PDS 100 mg/mL and ITV 0.5 mg.

	Unit	PDS 100 mg/mL	ITV 0.5 mg	Relative exposure PDS/ITV
AUCt	pg/ml*day	53900	138000	0.392
Cmax	pg/ml	478	2360	0.202
Cmin	pg/ml	249	141	1.77

AUCt - AUC in the last PDS dosing interval (from 504 to 672 days). ITV: Intravitreal. PDS: Port Delivery System with ranibizumab.

Source: Table 14 in Applicant's population PK report

4.3 Summary of Serum Ranibizumab Concentrations (pg/mL) following PDS ranibizumab and IVT Ranbizumab from Studies GX28228 and GR40549

Table 10. Pharmacokinetic Parameters [Geometric Mean (CV%)] in PK Population with Exclusions, Study GX28228

Cohort	Refill Number	n[a]	C_{max} (pg/mL)	t_{max}[b] (day)	C_{trough} (pg/mL)	AUC_{Last}[c] (ng • day/mL)	$t_{1/2}$[d] (day)
PDS 10 mg/mL	Implantation	16	105.52 (258.0)	11.45 (0 – 688.1)	14.96 (76.4)	5.89 (225.1)	168.20 (163.3)
	All refills	40	91.47 (187.2)	4.87 (0 – 688.1)	11.58 (65.7)	3.43 (176.8)	162.36 (129.3)
PDS 40 mg/mL	Implantation	24	220.87 (46.4)	12.87 (0 – 86.0)	61.64 (95.8)	28.39 (107.6)	88.30 (46.7)
	All refills	61	297.61 (115.2)	6.71 (0 – 91.1)	105.07 (77.4)	22.93 (96.9)	118.87 (76.2)
PDS 100 mg/mL	Implantation	27	1080.69 (272.5)	29.01 (0.8 – 180.3)	129.63 (149.2)	90.83 (64.7)	119.07 (128.4)
	All refills	70	1131.01 (256.6)	6.97 (0.8 – 180.3)	62.19 (345.2)	66.12 (71.4)	143.87 (171.4)

AUC_{Last} = area under the concentration-time curve from dosing (implant or refill) to last observation before next refill or exiting the study; C_{max} = maximum concentration; C_{trough} = concentration at trough, before next refill; CV = coefficient of variation; PDS = Port Delivery System with ranibizumab; $t_{1/2}$ = half-life; t_{max} = time of maximum concentration

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

[a] For implantation n refers to number of patients; for all refills, n refers to number of refill cycles (implantation to first refill, first refill to second refill, etc.). The number of refill cycles per patient varies.

[b] Median (range) is reported.

[c] The interval between each refill cycle (implantation to first refill, first refill to second refill, etc.) is variable between patients.

[d] Apparent terminal half-life.

Source: Table 2 from Module 2.7.2 from BLA 761197

Table 11. Summary of Serum Ranibizumab Concentrations (pg/mL) by Cohort for Subjects in the PK-Evaluable Population, Study GR40549

PK-Evaluable Population
Protocol: GR40549

Analyte: RO4893594 Treatment: COHORT 1: GX28228 RBZ PD 100MG/ML (N=30)

Visit/Timepoint	Nominal Time (day)	n	Number of LTRs	Mean	SD	CV % Mean	Geometric Mean	CV % Geometric Mean	Median	Minimum	Maximum
DAY 1	0	3	0	181	104	57.7	159	71.5	173	80.6	289
WEEK 8	56	28	2	434	265	61.0	319	161	396	7.50	1400
WEEK 24	168	24	4	269	172	63.9	160	269	263	7.50	631
WEEK 32	224	23	4	419	324	77.1	206	421	387	7.50	1320
WEEK 48	336	23	4	262	173	66.1	151	282	249	7.50	624
WEEK 56	392	19	4	329	263	80.0	155	422	312	7.50	909
WEEK 72	504	3	0	420	414	98.7	207	489	378	27.6	853

Analyte: RO4893594 Treatment: COHORT 3: GX28228 RBZ PD 100MG/ML (N=3)

Visit/Timepoint	Nominal Time (day)	n	Number of LTRs	Mean	SD	CV % Mean	Geometric Mean	CV % Geometric Mean	Median	Minimum	Maximum
DAY 1	0	3	0	102	58.1	56.8	90.4	70.6	99.2	45.9	162
WEEK 8	56	1	0	551	NE	NE	551	NE	551	551	551
WEEK 24	168	3	0	311	118	37.8	297	39.5	293	204	437
WEEK 32	224	2	0	400	194	48.4	376	53.9	400	263	537
WEEK 48	336	2	0	341	151	44.4	324	48.5	341	234	448
WEEK 56	392	2	0	382	235	61.5	344	73.7	382	216	548

CV = coefficient of variation; LTR = Lower than reportable; LTR is same as BLQ, BLQ = Below Limit of Quantification; MQC = minimum quantifiable concentration; NE = not evaluable; NR = non-reportable. BLQ results at nominal time <=0 are set to 0, and BLQ results on post-dose samples are set to 7.5 pg/mL i.e. half of MQC value (15 pg/mL), and summary statistics are reported as: For a given treatment and sampling time point: if one-third or fewer values were BLQ, then all summary statistics are reported. If more than one-third values were BLQ, then only the median and maximum are reported, Geometric mean is reported if no zero observations, and other summary statistics are displayed as NR.

Note: Patients were excluded from this table if they had received prior intravitreal injections with bevacizumab, received intravitreal ranibizumab injections in the fellow eye, or received supplemental intravitreal ranibizumab injections.

Source: Table 6 from Module 2.7.2 from BLA 761197

Table 12. Summary of Ranibizumab Concentrations by Matrix, Study GR40549

		Geometric Mean (%CV) Ranibizumab Concentration in ng/mL					
PDS 100 mg/mL (2 mg Q24W)	Matrix	Day 1	Week 8	Week 24 prerefill-exchange	Week 32	Week 48 prerefill-exchange	Week 56
Cohort 1	Aqueous Humor (N=30)	723(154)	1380 (370)	608 (361)	772 (971)	347 (656)	482 (2470)
	n	3	26	24	23	21	20
	Serum (N=29)	0.159 (71.5)	0.320 (167)	0.160 (269)	0.206 (421)	0.151 (282)	0.155 (422)
	n	3	27	24	23	23	19

PDS = Port Delivery System with ranibizumab; Q24W = every 24 weeks
N = number of patients; n = number of samples at a given timepoint

Source: Table 7 from Module 2.7.2 from BLA 761197

4.4 Summary of PK relevant Study Design Aspects for GR40548

Study GR40548 studied the final TBM product at the proposed dosing regimen of 2 mg (0.02 mL of 100 mg/mL solution) administered every 24 weeks (approximately 6 months). Study GR40548 is a Phase 3 multicenter, randomized, visual assessor-masked, active-comparator study designed to evaluate the efficacy, safety, and PK of PDS 100 mg/mL Q24W compared with IVT ranibizumab 0.5 mg injections Q4W in patients with nAMD. A total of 418 patients were enrolled and 415 patients were treated. Patients were randomized in a 3:2 ratio such that 248 patients received the PDS implant filled with 100 mg/mL ranibizumab Q24W (PDS 100 mg/mL arm) and 167 patients received monthly IVT injections of 0.5 mg (10 mg/mL) ranibizumab Q4W (IVT arm). Limited PK samples were taken from patients in the IVT arm because the serum PK of ranibizumab following IVT administration has been well characterized previously. Serum PK samples were collected at pre-dose before IVT injection from all patients in the IVT arm at all sites at the randomization visit and at Weeks 4, 24, 36, and 96. At selected sites, additional PK samples were collected from patients in the PDS 100 mg/mL arm on Days 2 and 7 and Weeks 12, 48, and 72. In addition, at selected sites, a serum PK sample was collected in patients in the IVT arm 1 to 5 days after an IVT ranibizumab 0.5 mg injection in order to collect a sample near Cmax. Aqueous humor PK samples were collected along with serum PK samples from patients who consented to this optional sampling in both treatment arms on Weeks 24, 28, 48, 52, 72, 76 and 96. In addition, mandatory aqueous humor samples were collected at the time of meeting supplemental treatment criteria and the subsequent study visit or at an early study termination visit or explant visit.

4.5 Summary of Immunogenicity Results from Study GR40548

The overall mean time of study was 80.0 weeks in the PDS 100 mg/mL arm and 78.5 weeks in the IVT arm through the clinical cut-off date (CCOD) (11 September 2020 CCOD). Based on this CCOD, incidence of treatment emergent ADA to ranibizumab was 29 of 247 patients (11.7%) and 10 of 165 patients (6.1%) in the PDS 100 mg/mL arm and intravitreal ranibizumab 0.5 mg arm, respectively (Table 13). A summary of the treatment-induced ADAs to ranibizumab is provided in Table 14.

Table 13. Baseline Prevalence and Incidence of Treatment Emergent Anti-Drug Antibodies

	RBZ PD 100MG/ML (N=248)	RBZ ITV SOC 0.5MG (N=167)	All subjects (N=415)
Baseline Prevalence of ADAs			
Baseline evaluable patients	243	162	405
Patients with a positive sample at time of entry into the study	5 (2.1%)	8 (4.9%)	13 (3.2%)
Patients with no positive samples at time of entry into the study	238	154	392
Incidence of Treatment Emergent ADA			
Post-baseline evaluable patients	247	165	412
Patients Positive for ADA	34	16	50
Patients positive for Treatment Emergent ADA	29 (11.7%)	10 (6.1%)	39 (9.5%)
Treatment-induced ADA	29	8	37
Treatment-enhanced ADA	0	2	2
Treatment unaffected or reduced	5	6	11
Patients negative for ADA at all times in the study	213	149	362

ADA = Anti-Drug Antibodies (is also referred to as ATA, or Anti-Therapeutic Antibodies)
Baseline evaluable patient = a patient with an ADA assay result from a baseline sample(s)
Post-baseline evaluable patient = a patient with an ADA assay result from at least one post-baseline sample
Number of patients positive for Treatment Emergent ADA = the number (and percentage) of post-baseline evaluable patients determined to have treatment-induced ADA or treatment-enhanced ADA during the study period.
Patients Positive for ADA = the number of post-baseline evaluable patients determined to have treatment-induced ADA, treatment-enhanced ADA or treatment unaffected ADA during the study period.
Treatment-induced ADA = a patient with negative or missing baseline ADA result(s) and at least one positive post-baseline ADA result.
Treatment-enhanced ADA = a patient with positive ADA result at baseline who has one or more post-baseline titer results that are at least 0.60 t.u. greater than the baseline titer result.
Number of patients negative for Treatment Emergent ADA = number of post-baseline evaluable patients with negative or missing baseline ADA result(s) and all negative post-baseline results, or a patient who is treatment unaffected.
Treatment unaffected = A post-baseline evaluable patient with a positive ADA result at baseline and (a) where all post-baseline titer results are less than 0.60 t.u. greater than the baseline titer result, OR (b) where all post-baseline results are negative or missing.
For any positive sample with titer result less than the minimum reportable titer or any positive sample where a titer cannot be obtained, titer value is imputed as equal to the minimum reportable titer.

Source: Table 5 of Integrated Summary of Immunogenicity Report from BLA 761197

Table 14. Treatment-Induced Anti-Drug Antibodies in Ranibizumab Intravitreal and Port Delivery System Treatment Arms

	RBZ PD 100MG/ML (N=248)	RBZ ITV SOC 0.5MG (N=167)	All Subjects (N=415)
Post-baseline evaluable patients	247	165	412
Patients with treatment-induced ADA	29 (11.7%)	8 (4.8%)	37 (9.0%)
Patients with transient ADA	6 (20.7%)	0	6 (16.2%)
Patients with persistent ADA	23 (79.3%)	8 (100%)	31 (83.8%)
Median time to onset of ADA (weeks)	23.12	24.88	23.95
ADA Titer range (min - max)	1.00 - 3.98	1.00 - 2.65	1.00 - 3.98

ADA = Anti-Drug Antibodies (is also referred to as ATA, or Anti-Therapeutic Antibodies)
Treatment-induced ADA = negative or missing baseline ADA result(s) and at least one positive post-baseline ADA result.
Transient ADA = ADA positive result detected (a) at only one post-baseline sampling timepoint (excluding last timepoint) OR (b) at 2 or more timepoints during treatment where the first and last ADA positive samples are separated by a period of < 16 weeks, irrespective of any negative samples in between.
Persistent ADA = ADA positive result detected (a) at the last post-baseline sampling timepoint, OR (b) at 2 or more time points during treatment where the first and last ADA positive samples are separated by a period = 16 weeks, irrespective of any negative samples in between.

Source: Table 6 of Integrated Summary of Immunogenicity Report from BLA 761197

The baseline prevalence and incidence of treatment-emergent NAbs to ranibizumab are provided in Table 15.

Table 15. Baseline Prevalence and Incidence of Treatment Emergent Neutralizing Antibodies (NAb)

	RBZ PD 100MG/ML (N=248)	RBZ ITV SOC 0.5MG (N=167)
Baseline Prevalence of NAbs		
Baseline evaluable patients for ADA	243	162
Patients with a positive ADA sample at time of study entry	5 (2.1%)	8 (4.9%)
Patients with no positive ADA samples at time of study entry	238	154
Baseline evaluable patients for NAb	5	8
Patients with a positive NAb sample at baseline	1 (20.0%)	2 (25.0%)
Patients with no positive NAb samples at baseline	4	6
Incidence of Treatment Emergent NAbs		
Post-baseline evaluable patients for ADA	247	165
Patients Positive for ADA	34	16
Patients positive for Treatment Emergent ADA	29 (11.7%)	10 (6.1%)
Post-baseline evaluable patients for NAb with Treatment Emergent ADA	28	9
Patients with Treatment Emergent ADA and positive for NAb	13	4
Patients with Treatment Emergent ADA and Negative for NAb	15	5
Patients with Treatment unaffected or reduced ADA	5	6
Post-baseline evaluable patients for NAb with Treatment unaffected /reduced ADA	4	6
Patients with Treatment unaffected or reduced ADA and positive for NAb	1	3
Patients with Treatment unaffected or reduced ADA and Negative for NAb	3	3

ADA = Anti-Drug Antibodies (is also referred to as ATA, or Anti-Therapeutic Antibodies)
Baseline evaluable patient = a patient with an ADA assay result from a baseline sample(s)
Post-baseline evaluable patient = a patient with an ADA assay result from at least one post-baseline sample
Number of patients positive for Treatment Emergent ADA = the number (and percentage) of post-baseline evaluable patients determined to have treatment-induced ADA or treatment-enhanced ADA during the study period.
Patients Positive for ADA = the number of post-baseline evaluable patients determined to have treatment-induced ADA, treatment-enhanced ADA or treatment unaffected ADA during the study period.
Number of patients negative for Treatment Emergent ADA = number of post-baseline evaluable patients with negative or missing baseline ADA result(s) and all negative post-baseline results, or a patient who is treatment unaffected.
Treatment unaffected = A post-baseline evaluable patient with a positive ADA result at baseline and (a) where all post-baseline titer results are less than 0.60 t.u. greater than the baseline titer result, OR (b) where all post-baseline results are negative or missing.
For any positive sample with titer result less than the minimum reportable titer or any positive sample where a titer cannot be obtained, titer value is imputed as equal to the minimum reportable titer.

	All subjects (N=415)
Baseline Prevalence of NAbs	
Baseline evaluable patients for ADA	405
Patients with a positive ADA sample at time of study entry	13 (3.2%)
Patients with no positive ADA samples at time of study entry	392
Baseline evaluable patients for NAb	13
Patients with a positive NAb sample at baseline	3 (23.1%)
Patients with no positive NAb samples at baseline	10
Incidence of Treatment Emergent NAbs	
Post-baseline evaluable patients for ADA	412
Patients Positive for ADA	50
Patients positive for Treatment Emergent ADA	39 (9.5%)
Post-baseline evaluable patients for NAb with Treatment Emergent ADA	37
Patients with Treatment Emergent ADA and positive for NAb	17
Patients with Treatment Emergent ADA and Negative for NAb	20
Patients with Treatment unaffected or reduced ADA	11
Post-baseline evaluable patients for NAb with Treatment unaffected or reduced ADA	10
Patients with Treatment unaffected or reduced ADA and positive for NAb	4
Patients with Treatment unaffected or reduced ADA and Negative for NAb	6

ADA = Anti-Drug Antibodies (is also referred to as ATA, or Anti-Therapeutic Antibodies)
Baseline evaluable patient = a patient with an ADA assay result from a baseline sample(s)
Post-baseline evaluable patient = a patient with an ADA assay result from at least one post-baseline sample
Number of patients positive for Treatment Emergent ADA = the number (and percentage) of post-baseline evaluable patients determined to have treatment-induced ADA or treatment-enhanced ADA during the study period.
Patients Positive for ADA = the number of post-baseline evaluable patients determined to have treatment-induced ADA, treatment-enhanced ADA or treatment unaffected ADA during the study period.
Number of patients negative for Treatment Emergent ADA = number of post-baseline evaluable patients with negative or missing baseline ADA result(s) and all negative post-baseline results, or a patient who is treatment unaffected.
Treatment unaffected = A post-baseline evaluable patient with a positive ADA result at baseline and (a) where all post-baseline titer results are less than 0.60 t.u. greater than the baseline titer result, OR (b) where all post-baseline results are negative or missing.
For any positive sample with titer result less than the minimum reportable titer or any positive sample where a titer cannot be obtained, titer value is imputed as equal to the minimum reportable titer.

Source: Table 7 of Integrated Summary of Immunogenicity Report from BLA 761197

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

/s/

AMIT A SOMANI
09/23/2021 02:40:09 PM

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