



# Pharmacokinetics of the Port Delivery System with Ranibizumab in the Ladder Phase 2 Trial for Neovascular Age-Related Macular Degeneration

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## ABSTRACT

**Introduction:** Ladder was a phase 2 trial that evaluated the Port Delivery System with ranibizumab (PDS) for neovascular age-related macular degeneration. Serum and aqueous humor samples were collected to characterize the pharmacokinetics (PK) of ranibizumab delivered through the PDS.

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**Methods:** Ladder was a multicenter, randomized, active treatment-controlled, phase 2 clinical trial. Patients with neovascular age-related macular degeneration ( $n = 220$ ) were randomized (3:3:3:2) to PDS 10 mg/ml, PDS 40 mg/ml, PDS 100 mg/ml, or monthly intravitreal ranibizumab 0.5 mg. Serum PK samples were collected in all arms and analyzed for ranibizumab concentration using an enzyme-linked immunosorbent assay. The main PK analyses were conducted in the PK-evaluable population ( $n = 68$ ), which excluded patients who received fellow eye intravitreal treatment, supplemental ranibizumab treatment, or had previous treatment with bevacizumab in either eye within 9 months of randomization.

**Results:** In the PDS 10 mg/ml arm, median serum ranibizumab concentrations were below the serum trough concentration ( $C_{\text{trough}}$ ; 130 pg/ml) expected with monthly intravitreal ranibizumab 0.5 mg at all time points. In the PDS 40 mg/ml and 100 mg/ml arms, median serum ranibizumab concentrations were above the  $C_{\text{trough}}$  expected with monthly intravitreal ranibizumab 0.5 mg (130 pg/ml) through month 3 and month 12 after implantation, respectively, and remained above the lower limit of quantification through month 15 and month 16 after implantation, respectively.

**Conclusions:** These PK data indicate that the implant in the PDS 100 mg/ml arm maintained ranibizumab concentrations within the range of monthly intravitreal ranibizumab 0.5 mg

injections (130–2220 pg/ml) through month 12 after implantation.

**Trial Registration:** ClinicalTrials.gov identifier, NCT02510794.

**Keywords:** Age-related macular degeneration; Implant; Neovascular age-related macular degeneration; Pharmacokinetics; Port Delivery System with ranibizumab; Ranibizumab; Vascular endothelial growth factor

### Key Summary Points

#### *Why carry out this study?*

Ladder was a phase 2 trial that evaluated the Port Delivery System with ranibizumab (PDS) for the treatment of neovascular age-related macular degeneration.

The PDS is a drug delivery system that consists of a refillable ocular implant for the continuous delivery of a customized formulation of ranibizumab into the vitreous.

During Ladder, serum and aqueous humor samples were collected to characterize the pharmacokinetics of ranibizumab delivered through the PDS.

#### *What was learned from this study?*

Concentrations achieved with PDS 100 mg/ml were within the same range as observed with monthly intravitreal ranibizumab dosing through month 12 following implantation, consistent with the comparable visual outcomes observed between the PDS 100 mg/ml and monthly intravitreal ranibizumab arms.

Serum ranibizumab concentrations following treatment with the PDS decreased at a slower rate than was observed previously following intravitreal injection, resulting in steadier concentrations over time with PDS treatment.

## INTRODUCTION

Intravitreal anti-vascular endothelial growth factor (VEGF)-A therapy is the standard of care for the treatment of neovascular age-related macular degeneration (nAMD) [1]. The anti-VEGF agent ranibizumab is a humanized monoclonal antibody antigen-binding fragment that inhibits all isoforms of VEGF-A [1, 2]. The pharmacokinetics (PK) of ranibizumab intravitreal injections for the treatment of nAMD [3] have been well characterized.

After intravitreal injection, ranibizumab demonstrates a phenomenon referred to as “flip-flop kinetics” [3]. For most drug classes, the absorption rate exceeds the elimination rate; however, flip-flop kinetics describes the reverse scenario: kinetics in which the absorption rate is significantly slower than the systemic elimination rate [4]. For ranibizumab, absorption from the vitreous to the systemic circulation is significantly slower than the systemic elimination rate (ocular and systemic half-lives [ $t_{1/2}$ ] are observed to be ~ 9 days and 2 h, respectively) [3]. This results in a depot effect, where the vitreous acts as a depot that slowly releases ranibizumab into systemic circulation, where it is quickly eliminated [3]. Because the ocular clearance is the rate-limiting step, the serum PK profile directly reflects the ocular PK profile, with serum concentrations being an estimated 90,000 times lower than vitreous concentrations [3]. From dosing to 30 days after monthly intravitreal ranibizumab 0.5 mg injections, serum ranibizumab concentrations range from 0.069 to 2.9 ng/ml [3]. Population PK analysis of ranibizumab administered via intravitreal injection has found renal impairment status to have a statistically significant, but clinically insignificant, effect on systemic elimination of ranibizumab, with a patient’s creatinine clearance explaining 10.5% of interindividual variability in ranibizumab systemic clearance [3].

In clinical trials of ranibizumab in which patients received monthly intravitreal injections, the serum PK profile consisted of peaks and troughs, with highest concentrations soon after the bolus dose and lowest concentrations before the next dose [3]. Within clinical trials,

maximal efficacy outcomes with anti-VEGF therapy appear to be achieved with consistent treatment at regular intervals [5–8]. In clinical practice, such outcomes have proven challenging to achieve because patients are, on average, treated less frequently [9–15], resulting in poorer vision outcomes compared with clinical trials [9–11, 13–15].

The Port Delivery System with ranibizumab (PDS) is a long-acting drug delivery system that consists of a permanent, indwelling refillable implant designed to provide continuous delivery of a customized formulation of ranibizumab into the vitreous [16] and maintain therapeutic drug concentrations in the vitreous for extended durations. The PDS implant can be refilled in the clinic using a specially designed refill-exchange needle [16]. The refill-exchange procedure ensures a near-total fluid exchange by simultaneously withdrawing the depleted drug remaining in the implant and injecting full-concentration drug. Based on *in vitro* characterization, a small percentage ( $\sim 1$ –2.5%) of the reservoir volume of 20  $\mu\text{l}$  is released through the release control element into the vitreous during the refill-exchange procedure. Ranibizumab release from the PDS implant into the vitreous is mediated by passive diffusion across a porous titanium release control element specifically designed for ranibizumab. *In vitro* studies have shown that ranibizumab release from the PDS implant is a function of concentration in the implant and decays exponentially over time, following Fick's law (data on file). Long-term stability evaluation demonstrated that ranibizumab did not show a difference in VEGF-blocking activity after incubation at 37 °C in phosphate-buffered saline supplemented with sodium azide and polysorbate 20 for 6 months [17].

The completed phase 2 Ladder trial (NCT02510794) evaluated the efficacy, safety, and PK of the PDS in patients with nAMD [16, 18]. Patients were randomized to receive one of three doses of ranibizumab via the PDS or monthly intravitreal ranibizumab 0.5 mg [16, 18]. The primary endpoint was median time to first criteria-defined implant refill, which was 8.7, 13.0, and 15.8 months for all patients in the PDS 10 mg/ml, PDS 40 mg/ml, and PDS 100 mg/ml arms, respectively, as

assessed at the end of the study [16, 18]. At months 6 and 12 after implant insertion, almost 80% and 60% of patients in the PDS 100 mg/ml arm, respectively, did not require refill-exchange procedures based on trial criteria [18].

Because the ranibizumab release rate from the implant is slow relative to both the ocular and systemic elimination rates [3], the serum PK profiles reflect the implant release. Preplanned PK analyses were conducted as part of the Ladder trial to characterize the PK profile of ranibizumab delivered through the PDS in patients with nAMD and are reported herein.

## METHODS

### Study Design and Participants

Full details of the Ladder trial (ClinicalTrials.gov identifier, NCT02510794) have been published [16, 18]. Briefly, Ladder was a phase 2, multicenter, randomized, active treatment-controlled, dose-ranging study of the PDS for nAMD conducted at 49 sites in the USA. The trial adhered to the tenets of the Declaration of Helsinki [19] and was conducted in accordance with the International Conference on Harmonisation E6 Guidelines for Good Clinical Practice [20] and with applicable local, state, and federal laws. All trial sites received institutional review board approval before trial initiation, and all patients provided written informed consent before enrollment.

Patients were aged  $\geq 50$  years and had anti-VEGF-responsive nAMD in the study eye diagnosed within the 9 months before screening. Patients had to have received  $\geq 2$  injections, but not more than 9 injections, with any anti-VEGF agent in the study eye. The previous injections could have been any anti-VEGF agent; however, the final injection before initiation of study treatment was ranibizumab. Patients were not excluded if they had nAMD in the fellow eye and were permitted to receive ranibizumab treatment, or another anti-VEGF therapy if clinically indicated, in that eye throughout the trial. Fellow eye treatment was not recommended within 7 days of the study eye scheduled visit.

Patients were assigned randomly 3:3:3:2 to treatment with the PDS filled with ranibizumab 10 mg/ml, 40 mg/ml, or 100 mg/ml formulations or to treatment with monthly intravitreal ranibizumab 0.5 mg injections (Lucentis®; Genentech, Inc., South San Francisco, CA, USA). The PK results described here do not include patients in the oral antithrombotic substudy, which included a separate trial population of 11 patients treated in the PDS 100 mg/ml arm.

For PDS patients, implant refills were performed on a pro re nata basis according to predefined criteria. Refill criteria for the PDS were assessed at each monthly visit [16].

Patients remained in the study until discontinuation or the decision was made to initiate rollover into the Portal trial, the open-label extension study for the PDS [18].

### Serum PK Sampling and Analysis of Ranibizumab Concentrations

All Ladder sites and patients participated in serum PK sampling; there was no specific PK substudy. In the PDS arms, serum samples for PK analysis were collected at randomization;  $\geq 60$  min after implant insertion; 1, 7, and 14 days after implant insertion; at each monthly study visit; and 1 and 7 days after each refill. Optional aqueous humor samples were collected from patients in the PDS arms before or immediately after implant refill and at 7 days after refill. In the monthly intravitreal ranibizumab 0.5 mg injection arm, serum trough concentration ( $C_{\text{trough}}$ ) samples were taken pre dose at randomization; months 1, 3, 6, and 9; and the final study visit.

Serum ranibizumab concentrations in all patients and aqueous humor ranibizumab concentrations in PDS-treated patients were measured using two validated enzyme-linked immunosorbent assays (ELISAs) described elsewhere [21], with lower limit of quantification (LLOQ) of 15 pg/ml for serum and 20,000 pg/ml for aqueous. The two assays were designed and optimized to have different quantitative ranges to better suit the range of ranibizumab concentrations expected to be found in those two

compartments [22]. Briefly, serum samples were incubated overnight with a mouse monoclonal anti-ranibizumab-VEGF complex antibody (MARA) and biotinylated VEGF; MARA-ranibizumab-biotinylated VEGF complexes were then captured on streptavidin-coated plates; finally, complexes were detected enzymatically using a horseradish peroxidase-conjugated antimouse antibody with colorimetric detection. For the aqueous samples, ELISA plates were coated with recombinant human VEGF, blocked with a bovine serum albumin buffer, and incubated with aqueous samples diluted to the assay minimum required dilution of 1/100 in sample diluent. After washing, plates were incubated for 2 h with a solution of F(ab')<sub>2</sub> fragment goat antihuman immunoglobulin G F(ab')<sub>2</sub> antibody conjugated to horseradish peroxidase. After washing, tetramethylbenzidine peroxidase substrate was added to the plate to develop color.

Analyses were conducted in the full study population and in the PK-evaluable population. The purpose of the analysis within the PK-evaluable population was to characterize the PK of the PDS, and thus it excluded patients whose serum and aqueous samples would not solely reflect ranibizumab release from the PDS implant. The purpose of the analysis within the full study population was to describe ranibizumab exposure in all treated patients in the study. The PK-evaluable population consisted of patients in the PDS arms only and excluded patients who received intravitreal ranibizumab injections in the fellow eye during the Ladder trial, supplemental intravitreal ranibizumab injections, or previous intravitreal injections with bevacizumab in either eye within 9 months before randomization. Patients who received supplemental intravitreal ranibizumab injections during Ladder were not included in the PK-evaluable population. Patients with previous intravitreal injections of bevacizumab were excluded because the ranibizumab ELISA also detects bevacizumab [21]. Bevacizumab has a  $t_{1/2}$  for systemic elimination of around 19 days and therefore may remain detectable in the systemic circulation for months after the last injection [23]. Patients who received previous

intravitreal aflibercept injections were not excluded from the PK-evaluable population.

### Endpoints and Analyses

The prespecified endpoints for the PK analysis of the Ladder trial included the observed maximum concentration ( $C_{\max}$ ) and selected post-dose serum concentrations immediately after implantation and all subsequent refills,  $C_{\text{trough}}$  before refills, and observed serum concentrations over time without refills in the PDS arms. Additional PK parameters, including area under the serum concentration-time curve extrapolated to infinity ( $AUC_{0-\text{inf}}$ ; calculated using the linear-up, log-down trapezoidal rule), time to  $C_{\max}$  ( $T_{\max}$ ),  $C_{\text{trough}}$ , and  $t_{1/2}$ , were estimated after implantation and at subsequent refills using standard noncompartmental analysis with Phoenix WinNonlin software, version 6.4 (Cetera, L.P., Princeton, NJ, USA). For mean serum concentration-time profiles, if more than one-third of values for a given arm and sampling time point were below the LLOQ, no value was reported. The geometric mean was used to summarize serum PK data when patients were grouped based on the same time since dosing, because it is reasonable to assume the data are log-normally distributed, as typical for PK data [24]. However, when summarizing data based on time on study, when patients were at different times relative to most recent refill, median was used to summarize serum PK data because a log-normal distribution can no longer be assumed.

A population PK model [3] was used to predict serum concentrations in the monthly intravitreal ranibizumab 0.5 mg group. The parameters for these model predictions were based on updated PK parameter estimates using data described previously [3] and additional data from the HARBOR clinical trial (NCT00891735). Model parameters were 3.3 l/d for typical systemic clearance, 3.27 l for typical apparent volume of the central compartment, and  $0.104 \text{ d}^{-1}$  for typical rate of vitreous elimination.

## RESULTS

### Patient Populations

The full efficacy analysis population of the Ladder trial consisted of 220 patients, with 58, 62, 59, and 41 patients in the PDS 10 mg/ml, PDS 40 mg/ml, PDS 100 mg/ml, and monthly intravitreal ranibizumab 0.5 mg injection arms, respectively [16]. Baseline demographics for the full study population have been described [16].

A total of 68 (38%) patients in the PDS arms were eligible for the PK-evaluable population, with 16, 25, and 27 patients in the PDS 10 mg/ml, PDS 40 mg/ml, and PDS 100 mg/ml arms, respectively. The numbers of patients meeting each of the exclusion criteria for the PK-evaluable population are tabulated in Table S1. The most frequent reason for exclusion from the PK-evaluable population was receiving intravitreal ranibizumab in the fellow eye after first study treatment. Baseline demographics for the PK-evaluable population are shown in Table 1 and were generally consistent with the demographics for the full study population [16]. The distribution of renal impairment status was consistent with previous PK analyses of ranibizumab administered via intravitreal injection in patients with nAMD [3]. In the PK-evaluable population, the mean time on study was 21.7 (range 14.8–36.0) months.

### Serum PK Profiles After Implant Insertion

Serum ranibizumab concentrations in the PK-evaluable population over time from implant insertion to first refill are shown in Fig. 1. Patient numbers decreased over time as patients received PDS refill-exchange procedures. In the PDS 100 mg/ml arm, serum ranibizumab concentration remained above the LLOQ through month 16. Geometric mean (coefficient of variation) serum concentrations in the PDS 100 mg/ml arm were 243 (146%), 160 (155%), 101 (137%), and 51 (108%) pg/ml at months 6, 9, 12, and 16, respectively. Through month 9, the geometric mean serum ranibizumab

**Table 1** Demographic and baseline characteristics of the Ladder pharmacokinetic population

Characteristic	Port Delivery System with ranibizumab 10 mg/ml ( <i>n</i> = 16)	Port Delivery System with ranibizumab 40 mg/ml ( <i>n</i> = 25)	Port Delivery System with ranibizumab 100 mg/ml ( <i>n</i> = 27)	All pharmacokinetic-evaluable patients ( <i>n</i> = 68)
Demographics				
Age (years)				
Mean (SD)	71.4 (8.9)	72.4 (9.4)	74.3 (7.8)	72.9 (8.6)
Range	56.0–84.0	50.0–88.0	57.0–87.0	50.0–88.0
Sex, <i>n</i> (%)				
Male	9 (56.3)	10 (40.0)	8 (29.6)	27 (39.7)
Lens status, <i>n</i> (%)				
Phakic	10 (66.7)	14 (58.3)	12 (46.2)	36 (55.4)
Pseudophakic	5 (33.3)	10 (41.7)	14 (53.8)	29 (44.6)
Renal impairment status				
Normal (CrCL $\geq$ 90 ml/min)	6 (37.5)	8 (33.3)	4 (14.8)	18 (26.9)
Mild impairment (60 $\leq$ CrCL < 90 ml/min)	7 (43.8)	10 (41.7)	14 (51.9)	31 (46.3)
Moderate impairment (30 $\leq$ CrCL < 60 ml/min)	3 (18.8)	5 (20.8)	8 (29.6)	16 (23.9)
Severe impairment (CrCL < 30 ml/min)	0	1 (4.2)	1 (3.7)	2 (3.0)

CrCL is estimated based on Cockcroft-Gault equation. Renal impairment status grouped based on US Food and Drug Administration guidance [25]

CrCL creatinine clearance, SD standard deviation

concentrations were within the range (130–2220 pg/ml) [3] expected with monthly intravitreal ranibizumab 0.5 mg injections, remaining above the expected  $C_{\text{trough}}$  and below the expected  $C_{\text{max}}$ . Serum ranibizumab concentrations following treatment with the PDS decreased at a slower rate than as observed previously following intravitreal injection, resulting in more steady concentrations over time with PDS treatment.

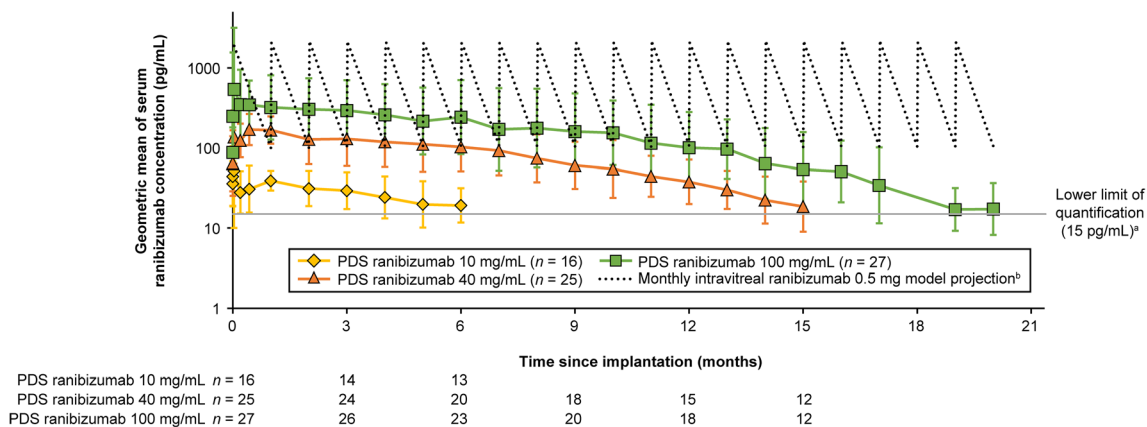
As expected, the serum ranibizumab concentrations were lower in the PDS 10 mg/ml and PDS 40 mg/ml arms but remained above the LLOQ at months 6 and 15, respectively. The geometric mean serum concentrations in the PDS 10 mg/ml

arm remained below the expected  $C_{\text{trough}}$  with monthly intravitreal ranibizumab 0.5 mg throughout the study; however, the geometric mean serum concentrations in the PDS 40 mg/ml arm were near the expected  $C_{\text{trough}}$  for the first 6 months after implant insertion.

PK parameters ( $C_{\text{max}}$ ,  $AUC_{0-\text{inf}}$ ,  $T_{\text{max}}$ ,  $C_{\text{trough}}$ ,  $t_{1/2}$ ) after implantation and all treatment cycles are reported in Table 2.

### Aqueous Humor Sample Correlation

Aqueous humor samples were collected from 6, 10, and 12 patients in the PK-evaluable



**Fig. 1** Serum pharmacokinetic (PK) profiles among PK-evaluable patients in the Port Delivery System with ranibizumab (PDS) arms without refill. Patient numbers decreased over time as patients received refills. Vertical bars represent the geometric standard deviation. Y axis is shown

on a logarithmic scale. <sup>a</sup>Lowe J, et al. J Immunol Methods. 2018;461:44–52 [21]. <sup>b</sup>Xu L, et al. Invest Ophthalmol Vis Sci. 2013;54:1616–24 [3]. Figure generated based on the updated population PK analysis (including data from the HARBOR clinical trial [NCT00891735])

population in the PDS 10 mg/ml, PDS 40 mg/ml, and PDS 100 mg/ml arms, respectively, before or immediately after refill and 7 days after refill. Aqueous humor ranibizumab concentrations in these samples correlated with mean serum ranibizumab concentrations in all three PDS arms (Fig. S1).

### Serum PK Profiles After Refill-Exchange

In the PDS 100 mg/ml arm, the serum PK profile was consistent after implantation and multiple refills (Fig. 2). At 6 months after implantation or the first refill-exchange procedure, geometric mean (coefficient of variation) serum ranibizumab concentrations were 243 (146%) and 227 (32.7%) pg/ml, respectively. Serum PK profiles after refill-exchange procedures were also consistent with the profiles after implantation in the PDS 10 mg/ml and PDS 40 mg/ml arms (Fig. S2a and S2b).

### Serum PK Profiles in the Full Study Population over the Course of the Trial (Independent of When Refill Occurred)

In the full Ladder trial study population, ranibizumab serum concentrations in the PDS

100 mg/ml arm were within the range expected with the PK model of monthly intravitreal ranibizumab injections (Fig. 3). The PK model for monthly intravitreal ranibizumab injections was generally consistent with the observed  $C_{trough}$  values in the monthly intravitreal ranibizumab 0.5 mg arm, with the model predicting slightly higher  $C_{trough}$  values than observed. At month 9, the last consistent time point at which serum samples were collected in all monthly intravitreal ranibizumab 0.5 mg patients, median ranibizumab serum concentrations were 27.9, 110, 235, and 56.1 pg/ml for the PDS 10 mg/ml, PDS 40 mg/ml, PDS 100 mg/ml, and monthly intravitreal ranibizumab 0.5 mg arms, respectively.

## DISCUSSION

This PK-evaluable population of the phase 2 Ladder trial demonstrated that the serum concentrations of ranibizumab with PDS 100 mg/ml were within the range expected with monthly intravitreal ranibizumab 0.5 mg through at least month 9, remaining above the expected  $C_{trough}$  and below the expected  $C_{max}$ . In addition, PDS 100 mg/ml continued to release ranibizumab through at least month 16, after which time, the serum concentration

**Table 2** Pharmacokinetic parameters in the pharmacokinetic-evaluable population

Geometric mean (CV%)	Port Delivery System with ranibizumab 10 mg/ml		Port Delivery System with ranibizumab 40 mg/ml		Port Delivery System with ranibizumab 100 mg/ml	
	Implantation	All treatment cycles	Implantation	All treatment cycles	Implantation	All treatment cycles
$n^a$	16	40	24	61	27	70
$C_{max}$ (pg/ml)	105.52 (258.0)	91.47 (187.2)	220.87 (46.4)	297.61 (115.2)	1080.69 (272.5)	1131.01 (256.6)
$AUC_{0-inf}$ (d*ng/ml)	12.43 (124.0)	10.47 (99.9)	38.91 (63.4)	44.93 (65.4)	141.52 (42.6)	140.66 (62.3)
$T_{max}^b$ (d)	11.45 (0–688.1)	4.87 (0–688.1)	12.87 (0–86.0)	6.71 (0–91.1)	(0.8–180.3)	6.97 (0.8–180.3)
$C_{trough}$	14.96 (76.4)	11.58 (65.7)	61.64 (95.8)	105.07 (77.4)	129.63 (149.2)	62.19 (345.2)
$t_{1/2}^c$	168.20 (163.3)	162.36 (129.3)	88.30 (46.7)	118.87 (76.2)	119.07 (128.4)	143.87 (171.4)

Pharmacokinetic-evaluable population with exclusions. Parameters are geometric means (geometric mean [CV%]) unless otherwise noted

$AUC_{0-inf}$  area under the serum concentration-time curve extrapolated to infinity,  $C_{max}$  maximum concentration,  $C_{trough}$  serum trough concentration,  $CV$  coefficient of variation,  $t_{1/2}$  half-life,  $T_{max}$  time to maximum concentration

<sup>a</sup>For implantation,  $n$  refers to the number of patients; for all treatment cycles,  $n$  refers to the number of refill treatment cycles (implantation to first refill, first refill to second refill, etc.). The number of refill cycles per patient varies

<sup>b</sup>Median (range) is reported

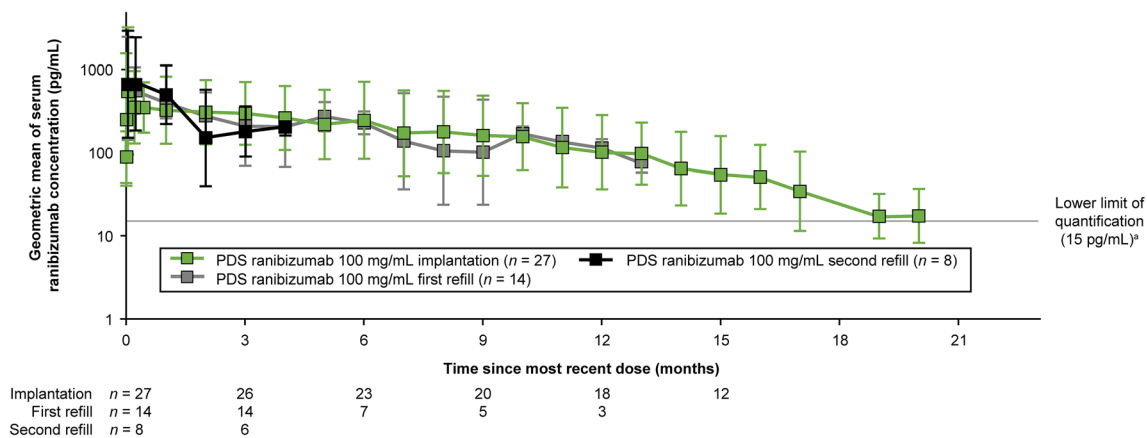
<sup>c</sup>Apparent terminal  $t_{1/2}$

approached the LLOQ. Additionally, within each PDS arm, the serum PK profiles of ranibizumab were consistent after initial implantation and multiple refills. The PK-evaluable population was thoughtfully defined to exclude patients with confounding factors for the serum PK measurements that impact assessment of the PDS implant release. Many of the patients in the full study population were not eligible for the PK-evaluable population.

Extensive serum sampling was employed in all patients, providing a robust data set (5790 samples) for characterization of the PDS serum PK profile for ranibizumab. The PK profile of the full study population independent of time to refill in combination with the clinical outcome data demonstrate that PDS 100 mg/ml was able to deliver ranibizumab at levels that resulted in

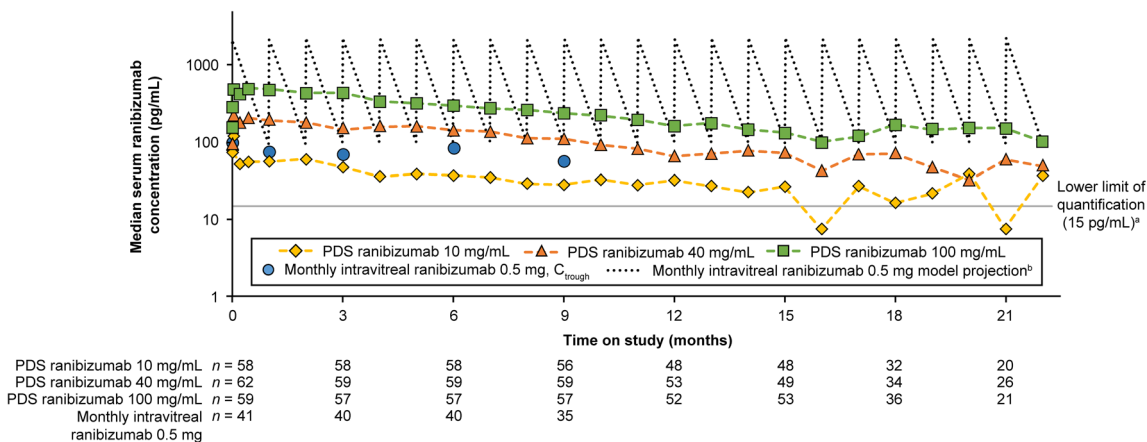
efficacious ocular ranibizumab concentrations for an extended period of time. The serum concentrations with PDS 100 mg/ml were within the range predicted for monthly intravitreal ranibizumab 0.5 mg, the dose approved for the treatment of nAMD, based on data from previous clinical trials [5, 8]. PDS 100 mg/ml PK serum concentrations were also consistently higher than the  $C_{trough}$  values observed in the Ladder monthly intravitreal ranibizumab 0.5 mg arm until month 9, when PK sampling stopped in this arm. These results support the durability of the treatment effects observed with the PDS in the Ladder trial. At the median first time to refill of 15.8 months in the PDS 100 mg/ml arm [18], ranibizumab was still being released from the PDS implant, as supported by the measurable serum ranibizumab concentrations at month 16 in this arm.





**Fig. 2** Serum pharmacokinetic (PK) profiles of PK-evaluable patients in the Port Delivery System with ranibizumab (PDS) 100 mg/ml arm after implantation,

first refill, and second refill. Vertical bars represent the geometric standard deviation. <sup>a</sup>Lowe J, et al. J Immunol Methods. 2018;461:44–52 [21]



**Fig. 3** Serum pharmacokinetic (PK) profiles through month 22 in the full study population, independent of refill time. Median (rather than geometric mean) is reported due to the variable timing of refill, and thus a log-normal distribution is not expected. <sup>a</sup>Lowe J, et al. J Immunol Methods. 2018;461:44–52 [21]. <sup>b</sup>Xu L, et al. Invest Ophthalmol Vis

Sci. 2013;54:1616–24 [3]. Figure generated based on the updated population PK analysis (including data from the HARBOR clinical trial [NCT00891735]).  $C_{trough}$  serum trough concentration, PDS Port Delivery System with ranibizumab

In clinical trials using intravitreal ranibizumab injections, there is variability in how frequently patients need treatment to maintain vision or anatomical outcomes [6, 7, 26]. This variability may be driven by a variety of patient and disease state factors, of which PK variability is only one component. Therefore, the ongoing ranibizumab concentrations needed to maintain clinical efficacy in an individual patient and in an individual eye likely vary. Although

systemic suppression of VEGF was not measured in this study, the serum ranibizumab concentrations with the PDS were maintained below the  $C_{max}$  for monthly intravitreal ranibizumab 0.5 mg injections, which have been shown to have a minimal impact on plasma-free VEGF levels [27]. Furthermore, serum ranibizumab concentrations with the PDS were below the concentrations (11,000–27,000 pg/ml) thought to be necessary to inhibit VEGF biological

activity by half [3] and the  $C_{\max}$  for intravitreal ranibizumab 2.0 mg injections was the highest intravitreal dose of ranibizumab clinically demonstrated to be well tolerated [6, 26].

Aqueous humor PK concentrations for ranibizumab with the PDS were consistent with the serum PK concentrations and consistent with flip-flop kinetics. However, it should be noted that collection of aqueous humor samples was optional in the Ladder trial and not all sites or patients contributed samples; in addition, aqueous humor samples were collected at a limited number of time points (i.e., limited longitudinal data), and the samples that were collected were at different times across patients due to the variable timing of refill in each patient. Thus, the PK data from the aqueous humor are not as thorough as the presented serum data.

There are several considerations for the current study. The length of time on study, timing of refills, and number of refills each patient received were variable, resulting in more limited PK assessment at later time points and after more refills. Because patients who received supplemental intravitreal ranibizumab injections were excluded from the PK-evaluable population and lower ranibizumab concentrations could have been the reason these patients met the lack of clinical efficacy criteria to require supplemental intravitreal ranibizumab injections, the observed concentrations in the PK-evaluable population may be affected by a selection bias. Furthermore, characterization of ranibizumab release at later times in the lower-dose arms was limited by the assay sensitivity. Finally, additional analyses and future studies will continue to build our understanding of the relationship between drug concentrations and clinical response.

## CONCLUSIONS

In conclusion, the PK profile of the PDS is consistent with the durability and clinical efficacy outcomes observed in the Ladder trial. PDS 100 mg/ml continuously releases ranibizumab through at least month 16, with serum PK profiles that are consistent after implantation and

multiple refills. Furthermore, the serum concentrations with PDS 100 mg/ml are within the range of concentrations achieved with monthly intravitreal ranibizumab 0.5 mg injections through  $\geq 10$  months after implantation. The PK and clinical findings from the Ladder clinical trial [16, 18], and results from the pivotal phase 3 Archway trial (NCT03677934) [28], which studied the efficacy and safety of PDS 100 mg/ml with fixed refill-exchanges every 24 weeks, support that PDS 100 mg/ml permits the continuous delivery of a clinically effective levels of ranibizumab for extended periods of time.

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**Compliance with Ethics Guidelines.** The trial adhered to the tenets of the Declaration of Helsinki [19] and was conducted in accordance with the International Conference on Harmonisation E6 Guidelines for Good Clinical Practice [20] and with applicable local, state, and federal laws. All trial sites received

institutional review board approval before trial initiation, and all patients provided written informed consent before enrollment.

**Data Availability.** For eligible studies, qualified researchers may request access to individual patient-level data through the clinical study data request platform. At the time of writing this request platform is Vivli (<https://vivli.org/ourmember/roche/>). For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: [https://go.roche.com/data\\_sharing](https://go.roche.com/data_sharing). Anonymized records for individual patients across > 1 data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient reidentification.

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