

The Port Delivery System with ranibizumab: a new paradigm for long-acting retinal drug delivery

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ABSTRACT

The Port Delivery System with ranibizumab (PDS) is an innovative intraocular drug delivery system designed for the continuous delivery of ranibizumab into the vitreous for 6 months and beyond. The PDS includes an ocular implant, a customized formulation of ranibizumab, and four dedicated ancillary devices for initial fill, surgical implantation, refill-exchange, and explantation, if clinically indicated. Ranibizumab is an ideal candidate for the PDS on account of its unique physicochemical stability and high solubility. Controlled release is achieved via passive diffusion through the porous release control element, which is tuned to specific drug characteristics to accomplish a therapeutic level of ranibizumab in the vitreous. To characterize drug release from the implant, release rate was measured *in vitro* with starting concentrations of ranibizumab 10, 40, and 100 mg/mL, with release of ranibizumab 40 and 100 mg/mL found to remain quantifiable after 6 months. Using a starting concentration of 100 mg/mL, active release rate at approximately 6 months was consistent after the initial fill and first, second, and third refills, demonstrating reproducibility between implants and between multiple refill-exchanges of the same implant. A refill-exchange performed with a single 100- μ L stroke using the refill needle was shown to replace over 95% of the implant contents with fresh drug. *In vitro* data support the use of the PDS with fixed refill-exchange intervals of at least 6 months in clinical trials.

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Introduction

Neovascular age-related macular degeneration (nAMD) is a chronic, progressive retinal disease and a leading cause of irreversible vision loss in adults aged 50 years and older, despite widespread availability and use of anti-vascular endothelial growth factor (VEGF) therapy (Flaxman et al., 2017; Wyckoff et al., 2018; Flaxel et al., 2020a). Diabetic retinopathy (DR) and associated diabetic macular edema (DME) are also major contributors to vision loss globally, with DR a principal cause of preventable blindness in working-age adults in the United States (Mohamed et al., 2007; Cheung et al., 2010; Flaxman et al., 2017). Anti-VEGF therapy is the current first-line standard of care for treating nAMD and DME, and an effective treatment option for proliferative DR (Flaxel et al., 2020a, 2020b). Anti-VEGF drugs currently approved and used in ophthalmology are ranibizumab, aflibercept, and brolucizumab (Lucentis [package insert], 2018; Eylea [package insert], 2019; Beovu [package insert], 2020). However, optimal vision outcomes are only achieved with frequent injections and monitoring (Campochiaro et al., 2019). This high frequency of treatment and monitoring places a considerable burden on patients, caregivers, and clinicians; regular clinic

visits (as often as monthly) are a challenge to maintain (Prenner et al., 2015; Maguire et al., 2016) and a frequent source of anxiety for patients (Senra et al., 2017). In the real world, undertreatment results in visual outcomes that fall short of clinical trial results (Maguire et al., 2016; Ciulla et al., 2020). There is significant unmet need for consistent treatment to the retina to achieve and maintain vision gains while reducing treatment frequency (Campochiaro et al., 2019).

The requirement for frequent injections of anti-VEGF therapy reflects the short intraocular half-life of these biologic agents, and the development of long-acting ocular drug delivery strategies has proved difficult (reviewed in Kim and Woo (2021)). Despite advances in the field, only a few technologies have been assessed in clinical trials, and only one, the Port Delivery System with ranibizumab (PDS; commercially available as Susvimo, Genentech, Inc., South San Francisco, CA), has progressed to late-stage investigation and subsequent approval from the US Food and Drug Administration (FDA; Kim and Woo, 2021; Clinicaltrials.gov, 2021b; Holekamp et al., 2022; Susvimo [package insert], 2021).

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The PDS is an innovative drug delivery technology that enables continuous delivery of a customized formulation of ranibizumab into the vitreous over extended periods of time. The PDS is the first permanent, refillable, ocular implant for the treatment of chronic retinal disease, recently FDA-approved for the treatment of nAMD in adults who have previously responded to at least two anti-VEGF injections. By reducing the need for monthly injections, and through controlled and sustained intravitreal VEGF suppression, it has the potential to reduce the treatment and monitoring burden in patients with retinovascular degeneration and retinovascular diseases and reduce the negative impact of undertreatment in clinical practice (Campochiaro et al., 2019; Khanani et al., 2020, 2021; Holekamp et al., 2022).

A phase 1 study (NCT01186432; Clinicaltrials.gov, 2021e) conducted with a PDS prototype filled with ranibizumab 10 mg/mL (commercially available as Lucentis, Genentech, Inc., South San Francisco, CA) in patients with nAMD demonstrated vision and implant functionality outcomes supportive of further investigation (Loewenstein et al., 2020). The phase 2 Ladder trial (NCT02510794; Clinicaltrials.gov, 2021g) compared the PDS implant filled with 1 of 3 ranibizumab dose concentrations (10, 40, 100 mg/mL) with pro re nata refills vs monthly intravitreal ranibizumab 0.5 mg injections in patients with nAMD. Visual and anatomic outcomes in the PDS 100 mg/mL arm were comparable with monthly intravitreal ranibizumab 0.5 mg injections and approximately 80% of patients went at least 6 months without meeting refill criteria (Campochiaro et al., 2019; Khanani et al., 2020). Archway (NCT03677934) was a phase 3 randomized open-label trial of the PDS in patients with nAMD (Clinicaltrials.gov, 2021b). Archway met its primary endpoint, demonstrating that PDS 100 mg/mL with fixed refill-exchanges every 6 months was both clinically equivalent and noninferior to monthly intravitreal ranibizumab 0.5 mg injections in terms of vision at the average of weeks 36 and 40 (Holekamp et al., 2022).

This manuscript provides an overview of the development of the Port Delivery Platform (PD-P). It describes findings from *in vitro* studies performed before the phase 2 and phase 3 clinical trials of the PDS; characterization of ranibizumab release from the PDS implant, reproducibility of ranibizumab release after refill-exchange, and refill-exchange efficiency of the PDS implant and refill needle.

Materials and methods

Experimental setup

Implants were filled with ranibizumab 10, 40, or 100 mg/mL before being individually suspended on custom-designed hangers and placed in 1.5-mL polypropylene tubes containing 300 μ L of phosphate buffered saline (PBS). PBS was used to model vitreous humor because it approximately matches the expected pH (7.0–7.4; Sobolewska et al., 2017) and osmolality (286.6–292.5 mOsmol/kg; Kokavec et al., 2016); it also contained 0.01% (w/v) polysorbate 20 to reduce protein loss due to adsorption and 0.02% (w/v) sodium azide to avoid bacterial contamination during the drug release study. Experimental setup is shown in Figure 1.

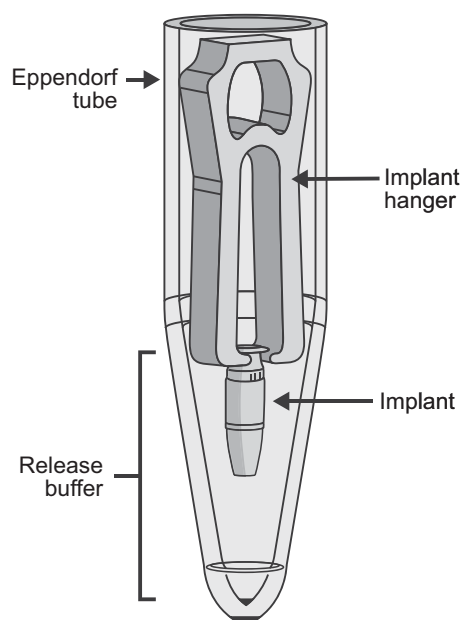


Figure 1. Schematic of experimental setup for *in vitro* evaluation of ranibizumab release from the PDS implant. To enable *in vitro* evaluation of drug release, PDS implants were filled with ranibizumab solution and individually suspended on custom-designed hangers, placed in 1.5-mL polypropylene tubes containing 300 μ L of release buffer. Implants were transferred to new polypropylene tubes with fresh buffer at regular intervals to maintain sink conditions for ranibizumab release. Abbreviation: PDS: Port Delivery System with ranibizumab. Yohe S, Maass KF, Horvath J, Rea J, Barteselli G, Ranade SV. *J Control Release.* 2022;345:101–107. Licensed under CC-BY-NC-ND 4.0 (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).

Implants were incubated at physiological temperature (34 °C; Landers et al., 2012) during drug release. The implants were transferred to new polypropylene tubes with fresh buffer weekly during the first month, and every other week thereafter, to represent ocular ranibizumab clearance and sustain release kinetics similar to that expected *in vivo*. Notably, ranibizumab release from the implant is slow compared with ocular and systemic elimination (half-lives are ≥ 100 days, ~ 7 days, and ~ 2 h in the implant, vitreous, and serum, respectively; Yohe et al., 2022). Due to drug clearance, there is no drug accumulation in the vitreous; thus, drug release from the PDS will proceed under sink conditions. Experiments were designed to simulate rather than duplicate *in vivo* conditions, with sink conditions maintained to avoid any impact of release volume on release rates. Using 300 μ L of PBS resulted in drug concentrations lower than 500 μ g/mL in the release buffer, corresponding to at least a 150-fold lower drug concentration in the buffer than in the implant. The collected release buffer was kept at 2–8 °C until sample analysis.

Measurement of ranibizumab release and activity

Ranibizumab concentrations in release buffer were measured using the Coomassie-Plus (Bradford) Assay kit (Thermo Fisher Scientific Inc., Waltham, MA) using automated sample preparation. Drug concentration and volume were used to calculate a mean daily ranibizumab release rate at each timepoint. The VEGF-binding activity (potency) of ranibizumab released from implants was measured using a Surface Plasmon Resonance

assay (Biacore, Cytiva, Marlborough, MA), with results used to determine percentage and release rate of active ranibizumab. Release rate data were fit using an exponential model to mimic the expected first-order release kinetics of diffusion and were compared with predicted release rate kinetics.

Determining the efficiency of refill-exchange

The PDS implant was first filled with PBS buffer using an initial fill needle, then refilled using a primed refill needle attached to a 1-mL syringe containing ranibizumab drug product. To assess efficiency of refill-exchange across a range of refill volumes, 20, 40, 60, 80, or 100 μL of ranibizumab 100 mg/mL was delivered accurately by a high-precision syringe pump (Pump 11 Elite Programmable Syringe Pump, Harvard Apparatus, Holliston, MA). After refill, the implant content was collected using an empty 3/10-mL insulin syringe with a 29-gauge (G) needle inserted into the implant

septum. The collected sample was analyzed for ranibizumab content using ultraviolet-visible spectrophotometry (UV-VIS spectrophotometer, Model 8453, Agilent Technologies, Santa Clara, CA). Refill efficiency was calculated as the ratio of the ranibizumab concentration measured in the implant after refill vs the concentration of the fill solution.

The PDS implant and ancillary devices

The PDS includes a customized formulation of ranibizumab, an ocular implant, and four dedicated ancillary devices that are used for the initial fill with ranibizumab, surgical implantation, refill-exchange, and if clinically necessary, explantation (Figure 2(A–D)).

The PDS implant (Figure 2(A)) has four key features: an extrascleral flange that anchors the implant in the sclera, a self-sealing septum that allows for implant refills, a hollow implant body that forms the drug reservoir for the

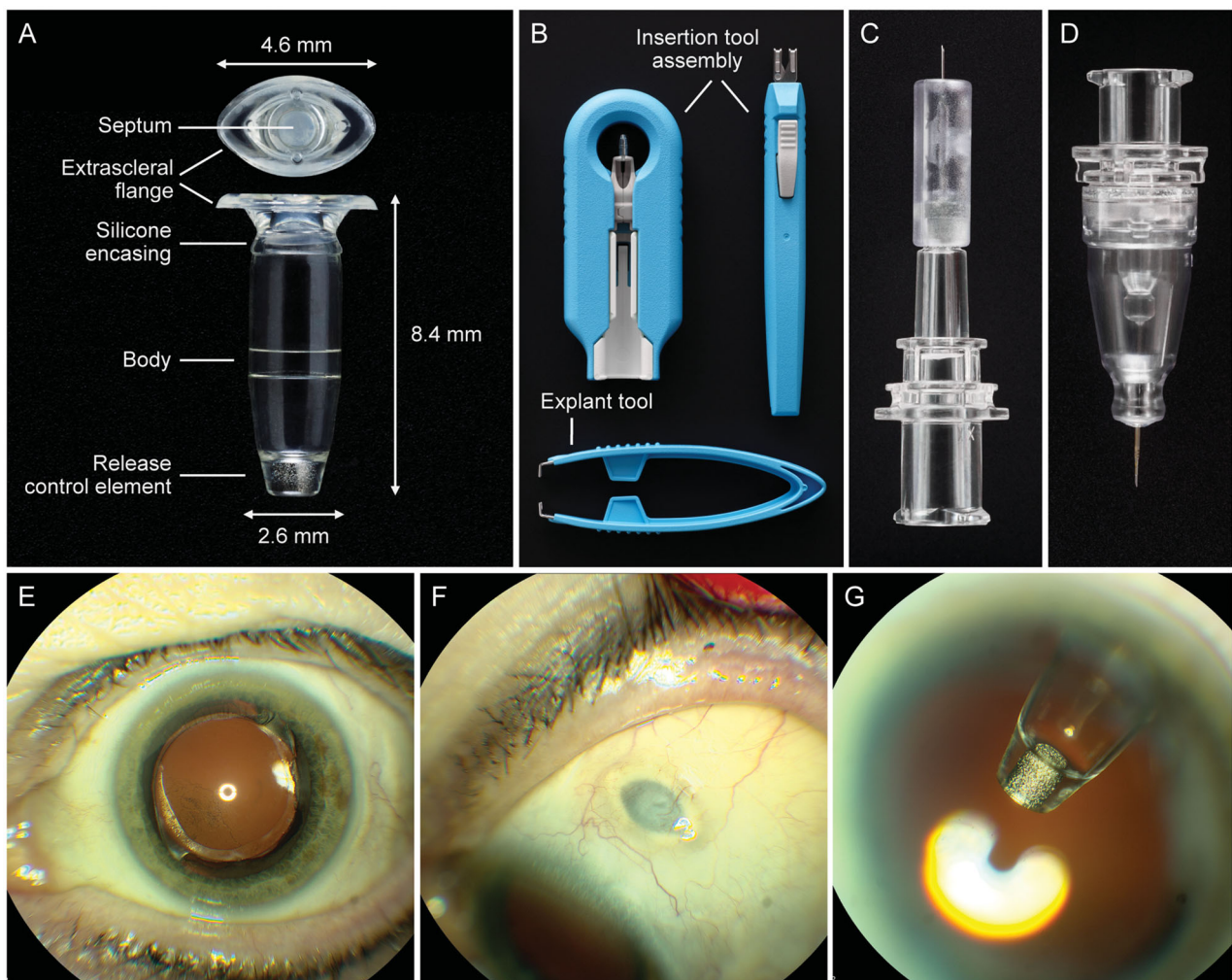


Figure 2. The PDS ocular implant, ancillary devices, and position *in situ*. (A) PDS implant showing four key features: an extrascleral flange that anchors the implant in the sclera, a self-sealing septum that allows for implant refills, an implant body that contains the drug reservoir for the customized formulation of ranibizumab, and the porous titanium RCE that controls the rate of ranibizumab diffusion into the vitreous. (B) Insertion tool assembly to facilitate handling of the implant during the initial filling and insertion procedures, and explant tool (lower image) to grasp and securely hold the implant flange during the explant procedure (if explantation is clinically indicated). (C) Initial fill needle to fill the implant with ranibizumab before insertion. (D) Refill needle to refill-exchange, *in situ*, the implant with ranibizumab. (E–G) show the PDS implant *in situ*. Images from a PDS-implanted patient showing (E) eye in primary position (implant not visible), (F) eye looking down with the PDS implant septum visible, and (G) eye looking up with implant visible through dilated pupil. Copyright 2021 F. Hoffmann-La Roche Ltd., all rights reserved. Used with permission. Abbreviations: PDS: Port Delivery System with ranibizumab; RCE: release control element.

customized ranibizumab formulation, and the porous titanium release control element (RCE) that controls the rate of ranibizumab diffusion into the vitreous. The implant has a capacity of approximately 20 μ L and is transparent to allow visualization of ranibizumab solution within the reservoir during initial fill. The septum is made of a self-sealing silicone, and is bonded to the implant body. The PDS implant is surgically placed at the pars plana and is intentionally designed to be biocompatible, permanent, and durable. The implant and extracts from the implant and ancillary devices have been determined to be nongenotoxic, noncytotoxic, nonsensitizing, and nonirritating (Bantsev et al., 2021). The drug reservoir and RCE reside within the vitreous, whereas the septum remains accessible under the conjunctiva and Tenon's capsule for minimally invasive in-clinic refill-exchanges. The implant has been designed to be noninterfering with the patient's field of vision and is covered by the eyelid; thus, it is not visible with the eye in primary gaze (Figure 2(E–G)).

The insertion tool assembly (Figure 2(B)) has a carrier design engineered to protect the implant during storage and handling, allowing simple, error-free, and ergonomic filling. The removable guide sleeve enables the implant to be filled with ranibizumab using the initial fill needle before insertion and, further, allows the attachment of the insertion tool handle to gripper tips to facilitate handling of the implant during the implant insertion procedure. The initial fill needle (Figure 2(C)) has a thin gauge (34G), with a custom length that precludes contact with the RCE while filling. The custom-designed refill needle (Figure 2(D)) allows for implant contents to be extracted simultaneously as the implant is filled with fresh ranibizumab during an in-office refill-exchange procedure (eVideo in the Supplement). The refill needle is a 34G double cannula, with a vented, custom-length needle and fluid collection reservoir. The explant tool (Figure 2(B); lower image) is used to remove the implant in the rare situation when explantation is clinically indicated. The tips of the explant tool are designed specifically to grasp the implant neck and flange securely without causing damage to the implant during removal.

The PDS implant and ancillary devices have evolved throughout the course of clinical development to optimize their performance and safety, with improvements made to both the materials and manufacturing procedures. Table 1 lists design changes that have been incorporated into the PDS commercial devices and procedures.

Drug compatibility with the Port Delivery System: suitability of ranibizumab

Specific drug characteristics are required for compatibility with the Port Delivery System implant and ancillary devices. The biologic drug must remain relatively stable within the implant to maintain potency and clinical safety between refills; isotonicity and high protein concentration are also critical. Ranibizumab is an ideal candidate for the Port Delivery System on account of its unique physicochemical stability in the vitreous, and its photostability and thermal stability in the implant under physiological conditions (34 °C), allowing it to stay in the implant for many months while remaining safe and effective (Chang et al., 2021; Rajagopal et al., 2021). Ranibizumab is highly water soluble and stable, and high-concentration solutions (up to 150 mg/mL) can be prepared with moderate to low viscosity for ease of implant filling and refilling.

Controlled release of ranibizumab is achieved via passive diffusion through the porous RCE. The drug diffusion follows Fick's law, wherein ranibizumab molecules move from an area of high concentration in the implant to low concentration in the vitreous cavity along a concentration gradient. The rate of diffusion is dependent on the ranibizumab concentration in the implant, which decreases over time. Diffusion, and thus drug release rate, is also controlled by the implant volume and RCE characteristics such as porosity and dimensions. The implant and ranibizumab formulation are designed to maintain drug concentration within therapeutic levels for the entire treatment cycle, with the RCE specifically tailored to the molecular weight and concentration of ranibizumab. The RCE must be tuned to specific drug characteristics, such as size, stability, and clearance, to accomplish a

Table 1. Evolution of the PDS implant and ancillary devices during clinical development.

Device	Changes	Purpose/Rationale
Implant	<ul style="list-style-type: none"> RCE changed to optimize delivery of high-concentration ranibizumab for 6 months and beyond RCE material changed from stainless steel to titanium Implant packaging changed to provide carrier that enables ergonomic fill 	<ul style="list-style-type: none"> Release rate target set to minimum of 2.3 μg/day at 6 months based on PK/PD simulations Titanium chosen for its corrosion resistance, MRI compatibility, and compatibility with the drug product New packaging minimizes handling of the implant and reduces the number of steps for use
Insertion tool	<ul style="list-style-type: none"> Improved design Material changed from stainless steel to plastic 	<ul style="list-style-type: none"> Increases ease of use for the initial fill of the implant with self-alignment features Implant release design is more ergonomic, robust, and intuitive Reduce weight of the tool for improved ergonomics and ease of use
Refill needle	<ul style="list-style-type: none"> Custom refill needle with fluid collection reservoir added to allow simultaneous exchange of the contents of the implant with fresh drug product 	<ul style="list-style-type: none"> The refill needle allows for removal of implant contents and minimizes the amount of drug bolus released into the vitreous humor during refilling of the implant
Explant tool	<ul style="list-style-type: none"> Material changed from stainless steel to plastic 	<ul style="list-style-type: none"> Improved manufacturability Reduce weight of the tool for improved ergonomics and increased ease of use

Abbreviations: MRI: magnetic resonance imaging; PDS: Port Delivery System with ranibizumab; PD: pharmacodynamic; PK: pharmacokinetic; RCE: release control element.

therapeutic level of drug in the vitreous; this is achieved via changes to the RCE porosity, tortuosity, and dimensions.

In vitro characterization of ranibizumab release and PDS refill-exchange

In vitro studies were performed to investigate the kinetics of ranibizumab release from the PDS implant, the reproducibility of ranibizumab release after refill-exchange, and the refill-exchange efficiency of the PDS implant and the refill needle. The aim of these studies was to provide further data to support the PDS implant as a feasible and effective means of administering ranibizumab intravitreally across multiple refill-exchanges.

Ranibizumab release from the PDS implant at different starting concentrations

The effect of initial ranibizumab concentration in the PDS implant was evaluated at 10, 40, and 100 mg/mL, showing increased starting mean (SD) drug release rates from 1.75 (0.07) to 16.69 (0.67) $\mu\text{g}/\text{day}$ (Figure 3). A starting concentration of 10 mg/mL resulted in ranibizumab concentrations below the lower limit of quantification within 2 months of filling. Starting concentrations of 40 and 100 mg/mL resulted in quantifiable drug release for longer than 6 months, with mean (SD) release rates at 6 months of 1.68 (0.05) and 4.16 (0.05) $\mu\text{g}/\text{day}$, respectively. These results demonstrate that drug release from the PDS implant is tunable by means of the starting concentration of the drug product. Ultimately, the phase 2 Ladder trial determined the ranibizumab concentration (100 mg/mL) and duration (time between refills) for subsequent clinical trials (Campochiaro et al., 2019; Khanani et al., 2020).

Active release rate after refill-exchange

The active release rate of ranibizumab 100 mg/mL *in vitro* was shown to be consistent across treatment cycles (Figure 4). The mean (SD) active release rate at 6 months was 3.95 (0.17), 3.99 (0.13), 3.85 (0.15), and 4.00 (0.17) $\mu\text{g}/\text{day}$ after initial fill, first, second, and third refill-exchanges, respectively, demonstrating reproducibility from implant to implant and between multiple refill-exchanges of the same implant.

Efficiency of refill-exchange

During the refill-exchange procedure (eVideo in the Supplement), previous implant contents were exchanged for fresh ranibizumab in a single injection stroke, with no significant bolus through the RCE during the procedure (Figure 5(A–F)). A single 100- μL refill-exchange procedure removed over 95% of the implant contents and replaced it with fresh drug (Figure 5(G)).

Discussion

Achieving and maintaining a therapeutic level of drug, whether biologic or small molecule, with long-term intraocular stability remains the biggest challenge in ocular drug delivery. Several strategies have been explored to enhance delivery efficiency by sustaining drug release, improving biocompatibility, and reducing potential for drug degradation, including molecular conjugation and formulation-based approaches (Kim and Woo, 2021).

A number of sustained release intravitreal steroid and small-molecule implants have been developed and approved for use in ocular disease indications, including Ozurdex (Allergan USA Inc., Madison, NJ; dexamethasone; biodegradable) for DME, retinal vein occlusion, and noninfectious uveitis; Iluvien (Alimera Sciences, Alpharetta, GA, USA) and

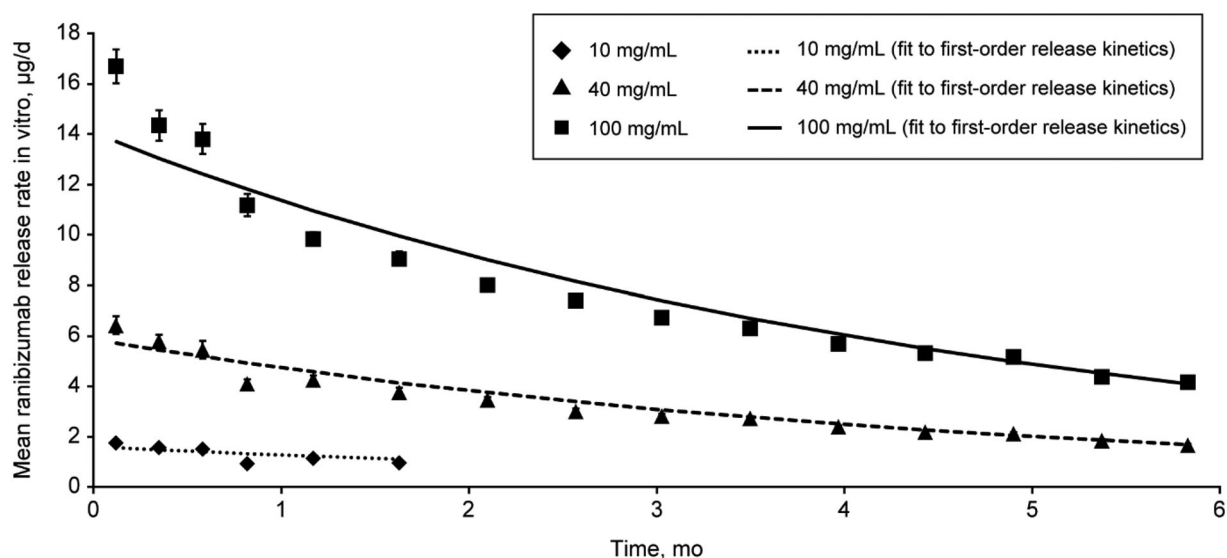


Figure 3. Mean ranibizumab release rate *in vitro* with the PDS 10, 40, or 100 mg/mL. Graph shows mean ranibizumab release rates *in vitro* in $\mu\text{g}/\text{day}$ over a period of 6 months, from PDS implants filled with ranibizumab at 10, 40, or 100 mg/mL. Dashed lines show theoretical drug release curves, calculated based on first-order drug release kinetics. Error bars show SD. Abbreviation: PDS, Port Delivery System with ranibizumab.

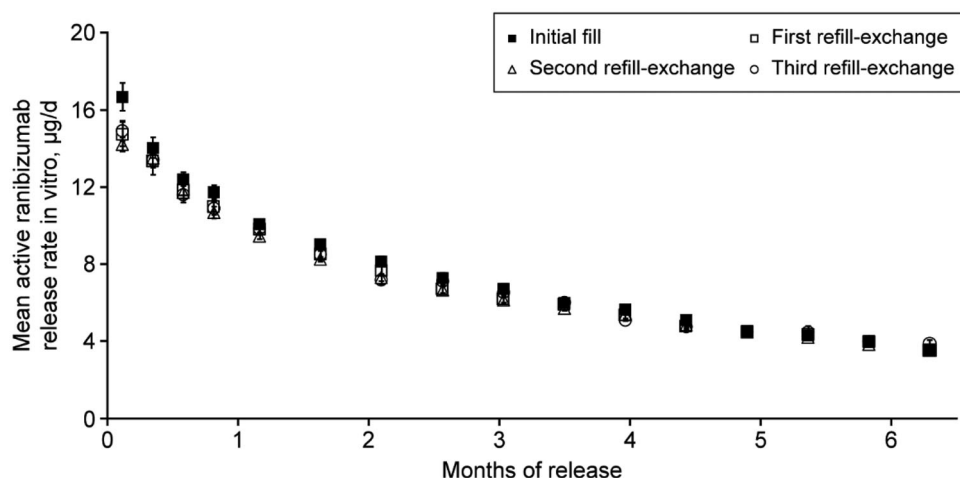


Figure 4. Mean ranibizumab release rate *in vitro* from the PDS 100 mg/mL after refill-exchange. Graph shows the mean active ranibizumab release rate *in vitro* in $\mu\text{g}/\text{day}$ from the PDS 100 mg/mL over a period of 6 months, after the initial fill, first, second, and third refill-exchange. Error bars show SD. Abbreviation: PDS: Port Delivery System with ranibizumab.

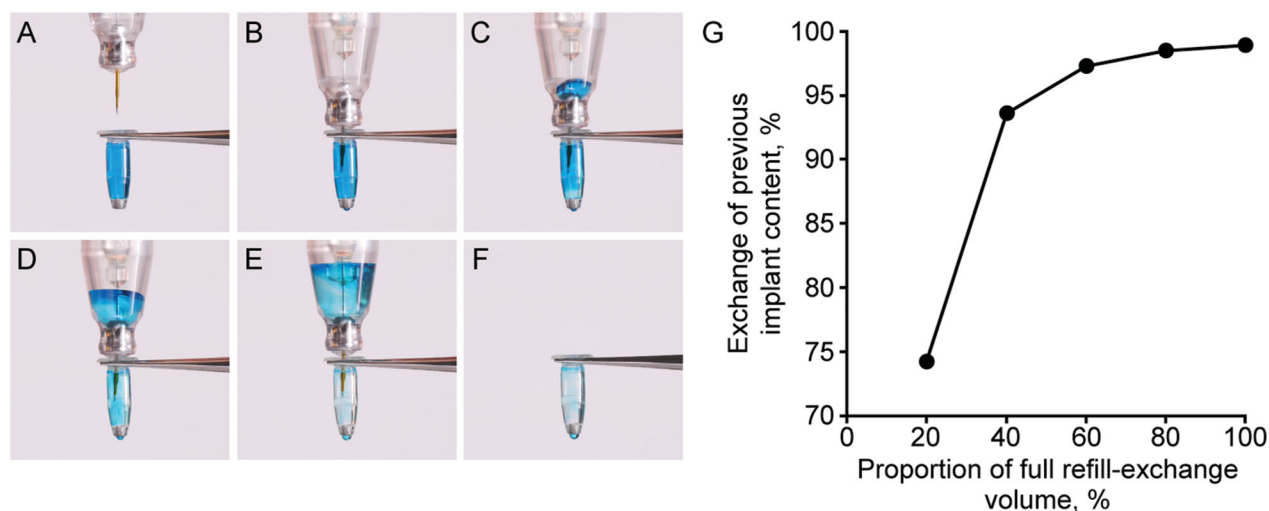


Figure 5. Refill-exchange of the PDS implant using the refill needle: procedure and efficiency. Images (A) to (F) show the sequential refill-exchange of the PDS implant using the refill needle, using a colored blue liquid as a proxy for previous implant contents. (G) shows the exchange of previous implant content when using 20–100% of the full refill-exchange volume. Copyright 2021 F. Hoffmann-La Roche Ltd., all rights reserved. Used with permission. Abbreviation: PDS: Port Delivery System with ranibizumab.

Retisert (Bausch + Lomb, Bridgewater, NJ)/Yutiq (EyePoint Pharmaceuticals US Inc., Watertown, MA; fluocinolone acetonide; nonbiodegradable) for DME and chronic noninfectious uveitis, respectively; and Vitrasert (Bausch + Lomb; ganciclovir; nonbiodegradable) for cytomegalovirus retinitis (Edelhauser et al., 2010; Iluvien [package insert], 2016; Ozurdex [package insert], 2020; Kim and Woo, 2021; US EP, 2021; Retisert [package insert], 2021). For sustained anti-VEGF therapy, implant-based systems tested in humans include the Ophthalmic MicroPump System (Replenish, Inc., Pasadena, CA; Humayun et al., 2014) and the encapsulated cell technology implant NT-503 (Neurotech Pharmaceuticals Inc., Cumberland, RI; Clinicaltrials.gov, 2021h), both of which did not progress beyond phase 1 clinical trials (Kiss, 2017; Seah et al., 2020).

The PDS is the first ocular implant to effectively deliver a biologic agent to the retina long term and offers the advantages of being permanent and refillable *in situ*. To date, the

PDS has demonstrated longevity, with the first patients enrolled in the Ladder trial now successfully retaining the implant since 2015, with no evidence of changing drug release characteristics of the RCE (Campochiaro et al., 2019; Khanani et al., 2020). Patient preference was evaluated during the Archway trial, with 93.2% of patients preferring ranibizumab as delivered via the PDS implant compared with intravitreal injection (Holekamp et al., 2022).

The *in vitro* analyses described here show that ranibizumab release from the PDS implant continues over 6 months and beyond, with a gradually decreasing rate over time, and that release rate can be tuned based on the starting concentration of the drug, with higher concentrations increasing the rate of release. Ranibizumab release rates are shown to be predictable and consistent after multiple refill-exchanges, and further, the refill-exchange procedure was found to be highly efficient, with successful replacement of over 95% of the implant contents.

Both the *in vitro* findings described here, and *in vivo* data from clinical trials, demonstrate that ranibizumab release from the PDS is continuous and reproducible across multiple refill-exchanges. In the Ladder trial, PDS 40 mg/mL and 100 mg/mL resulted in serum ranibizumab levels above the trough concentration observed with monthly injections at month 9 (Campochiaro et al., 2020). Further, pharmacokinetic data from the Archway trial show that serum ranibizumab levels in PDS 100 mg/mL patients are maintained within the range experienced with monthly injections over the 6-month refill-exchange interval. PDS 100 mg/mL also maintained aqueous humor ranibizumab levels above the trough concentration of monthly injections (Campochiaro et al., 2021). *In vitro* ranibizumab release rate and ranibizumab vitreal elimination rate can be used to predict vitreous ranibizumab concentration over time with the PDS (Yohe et al., 2022). Using this model, PDS 100 mg/mL would result in vitreous ranibizumab levels that remain within the levels expected with monthly intravitreal ranibizumab injections. Together, these results support the clinical efficacy of the PDS in Archway, with continuous ranibizumab delivery from the PDS 100 mg/mL every 24 weeks shown to provide equivalent and noninferior visual acuity outcomes compared with monthly injections (Holekamp et al., 2022).

Several large-scale clinical trials are currently investigating the PDS with ranibizumab 100 mg/mL. The phase 3 b Velodrome trial (NCT04657289; Clinicaltrials.gov., 2021c) is evaluating the efficacy, safety, and pharmacokinetics of the PDS with refill-exchange every 9 months compared with every 6 months in patients with nAMD, with the extension study Portal (NCT03683251; Clinicaltrials.gov., 2021d) evaluating the long-term safety and tolerability of the PDS in patients from Ladder, Archway, and Velodrome. Beyond nAMD, the phase 3 Pavilion trial (NCT04503551) is investigating the efficacy, safety, and pharmacokinetics of the PDS in patients with DR without DME (Clinicaltrials.gov., 2021a), and the phase 3 Pagoda trial (NCT04108156) is evaluating the PDS compared with monthly intravitreal ranibizumab injections in patients with DME (Clinicaltrials.gov., 2021i). These studies will include measurements of ranibizumab concentration in serum (and aqueous humor in Portal, Pagoda, and Pavilion) to further understand the relationship between ranibizumab concentration and efficacy. Data collection is still ongoing, but it is anticipated that these data will mirror the *in vivo* and *in vitro* findings from the Archway trial, with PDS 100 mg/mL found to continuously release ranibizumab over the 24-week refill interval, delivering drug concentrations within the range experienced with monthly ranibizumab 0.5 mg injections (Campochiaro et al., 2021).

Despite its advantages, the PDS may not be suitable for all patients, and patients and clinicians will make the informed choice between the PDS and intravitreal injections based on a number of variables. Patients must have demonstrated response to anti-VEGF therapies and be suitable candidates for surgery; factors such as ocular allergies, scleral disorders, and thin conjunctiva may mean that PDS implantation is not recommended. Importantly, ocular surgery carries some potential risks. For example, the FDA has issued a boxed

warning for the PDS due to association with a 3-fold higher rate of endophthalmitis compared with monthly intravitreal injections of ranibizumab (Susvimo [package insert], 2021). However, any ocular adverse events related to the PDS procedures are well understood, manageable, and are continually being analyzed to optimize patient outcomes (Holekamp et al., 2022). PDS surgical procedures have evolved based on trial learnings (Campochiaro et al., 2019; Bantsev et al., 2020), with an emphasis on surgeon training to standardize surgical techniques, supported by a state-of-the-art virtual reality training platform (Heimann et al., 2021).

The PD-P technology offers the potential to use other drugs, which should be carefully evaluated to ensure that they are suitable for continuous delivery (e.g. with adequate physicochemical characteristics) and are compatible with the implant and its RCE. A comparison of ranibizumab, bevacizumab, and aflibercept in PBS showed that although ranibizumab demonstrated long-term stability, bevacizumab and aflibercept were increasingly prone to aggregation over time, with loss of potency, suggesting that they are unlikely to be compatible with the PD-P (Chang et al., 2021; Rajagopal et al., 2021). In addition to stability and potency of a drug candidate, diffusion properties and solubility also play critical roles in achieving efficacious drug delivery rates from the PD-P. An ongoing phase 1 trial (NCT04567303) is currently investigating the safety, tolerability, and pharmacokinetics of RO7250284, a bispecific human antigen-binding antibody fragment that inhibits both angiopoietin-2 and VEGF, after intravitreal administration and via continuous delivery from the PD-P in patients with nAMD (Kirkner, 2021; Clinicaltrials.gov., 2021f). Further, there is the potential to alter the design of the RCE to enable the use of other drugs with the PD-P in the future, which may lead to novel options for the management of various ocular diseases.

Conclusions

The PDS is an innovative ocular drug delivery system, engineered to continuously and reproducibly deliver ranibizumab to the retina over an unprecedented period of at least 6 months; and is the first long-acting ocular biologic drug delivery system with demonstrated clinical safety and efficacy. Drug delivery of ranibizumab from the PDS implant is highly reproducible during *in vitro* studies, and has been demonstrated to be clinically effective in providing visual and anatomic outcomes comparable to monthly injections in nAMD with refill-exchange intervals of at least 6 months (Holekamp et al., 2022). These findings support the potential for the PDS to reduce the overall treatment and monitoring burden in clinical practice, with PDS regimens currently under investigation for patients with nAMD, DME, and DR. The Port Delivery System is a recently FDA-approved technology that delivers a biologic therapeutic to the eye over an extended period of time, with the potential to fundamentally change treatment paradigms in retinal diseases in the future.

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Author contributions

SVR had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Ranade, Tam, Rea, Horvath, Hieb.

Acquisition, analysis, or interpretation of data: Ranade, Wieland, Tam, Rea, Horvath, Hieb, Jia, Barteselli, Stewart.

Drafting and critical revision of the manuscript for important intellectual content: Ranade, Wieland, Tam, Rea, Horvath, Hieb, Jia, Grace, Barteselli, Stewart.

Supervision: Ranade

Meeting presentation

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Disclosure statement

Dr Ranade, Ms Tam, Dr Rea, Dr Horvath, Dr Hieb, Dr Jia, Ms Grace, and Dr Barteselli reported being employees of Genentech, Inc. Dr Wieland reported financial support from and being a consultant for Genentech, Inc.; and performing research for Genentech, Inc., Kodiak, Norlase, and Regeneron. Dr Stewart reported being a consultant for Genentech, Inc., Merck, Surrozen, and Valitor; and a personal financial interest in Roche.

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