Key Steps in the Optimisation of the Port Delivery System With Ranibizumab (PDS) Procedures and the Impact on Patient Outcomes

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Purpose

- To highlight some key steps of the PDS implant insertion procedure and adaptations implemented since the start of the trial programme and their impact on patient outcomes

Conclusions

Evolution of the PDS for Optimal Outcomes Includes Critical Updates to the Surgical Instructions for Use (IFU)

- Meticulous adherence to the 7-step surgical IFU is critical for surgical success
- Meticulous analyses of the implantation procedures and refills have led to a continuous evolution of PDS surgical procedures
- Trend toward reduction in key ocular AESI across PDS clinical trials may be consistent with improved surgical techniques

Implantations in clinical trials have resumed following improvements to manufacturing processes[a]

[a] Subject to local health authority approval.

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Introduction

- The PDS is a unique drug delivery system for continuous delivery of a customised formulation of ranibizumab into the vitreous
- The PDS implant insertion procedure has 7 critical steps, which have evolved during the clinical trial programme
- Following all surgical steps as described in the IFU is critical to maximise optimal surgical outcomes

Methods

PDS trials include:

- Ladder (NCT02510794), Archway (NCT03677934) and Portal (NCT03683251) in neovascular age-related macular degeneration (nAMD)
- Pagoda (NCT04108156) in diabetic macular oedema (DMO)
- Pavilion (NCT04503551) in diabetic retinopathy (DR)

Financial Disclosures

MM: None; AV: Employee: Hoffmann-La Roche AG; PJ: Employee: Roche Products Ltd.; CQR and NS: Employee and Stocks or Stock Options: Genentech, Inc.

Study and Product Disclosures

- The Port Delivery System with ranibizumab (PDS) has been approved by the US Food and Drug Administration for the treatment of nAMD in adults who have previously responded to ≥ 2 anti-VEGF injections. Please note that the PDS has not been approved for use outside of the United States
  - **Roche/Genentech voluntarily recalled the PDS (Susvimo) Ocular Implant and Insertion Tool Assembly, including the ranibizumab drug vial and initial fill needle (lot numbers 3499188 and 3523071), which are sold together. Roche/Genentech have restarted implantations in global clinical trials, subject to health authority and ethics committee approval**
- **The US Food and Drug Administration has issued a boxed warning for the PDS because it has been associated with a 3-fold higher rate of endophthalmitis compared with monthly intravitreal injections of ranibizumab[1]**
- This study includes research conducted on human subjects
- Institutional Review Board approval was obtained prior to study initiation
- Funding was provided by Genentech, Inc., a member of the Roche Group, for the study and third-party writing assistance, which was provided by Elizabeth Daniel, PhD, of Envision Pharma Group
- Roche conducted a factual accuracy check on the final article but any decision to incorporate comments was made solely at the discretion of the authors

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Results

Continuous Delivery Via the Port Delivery System With Ranibizumab

Innovative Drug Delivery System
- Refillable ocular implant for **continuous delivery** of a customised formulation of ranibizumab 100 mg/mL

PDS Implant and Refill
- Implanted surgically at the pars plana
- In-clinic refill-exchange procedures once or twice a year

Evolution of the PDS Surgical Procedures
- Key steps of the PDS implant insertion procedure
- Adaptations implemented since the start of the trial programme and continuously evolving



Images used with permission. Copyright © 2023 F. Hoffmann-La Roche Ltd. All rights reserved. PDS, Port Delivery System with ranibizumab.

Meticulous Adherence to the Instructions for Use May Mitigate Risks Associated With the PDS Implant Insertion Procedure

1 Case Preparation and Peritomy



6-mm x 6-mm dissection with wet cautery to achieve hemostasis

2 Implant Preparation



Fill implant with ranibizumab; prepare to implant

3 Scleral Dissection



Controlled 3.5-mm length cut down to pars plana

4 Laser Ablation of the Pars Plana



Endolaser probe to pretreat pars plana

5 Pars Plana Incision



3.2-mm stab incision through centre of sclerotomy

6 Implant Insertion



Implant seated in incision using custom tool

7 Conjunctival and Tenon's Closure

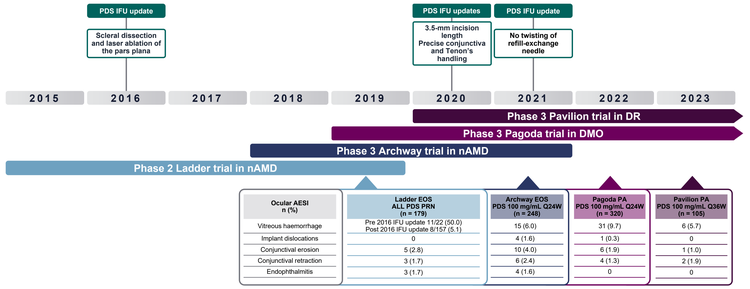


Suture both the conjunctiva and Tenon's capsule

Surgical complications associated with the PDS implant insertion procedure:
- Conjunctival erosion/retraction
- Endophthalmitis[a]
- Implant dislocation
- Conjunctival bleb
- Vitreous haemorrhage
- Implant dislocation
- Retinal detachment

[a] The FDA has issued a boxed warning for the PDS because it has been associated with a 3-fold higher rate of endophthalmitis compared with monthly intravitreal injections of ranibizumab.[1] FDA, US Food and Drug Administration; PDS, Port Delivery System with ranibizumab.

Key Updates to the Surgical "Instructions for Use" and AEs Observed Across PDS Clinical Trials



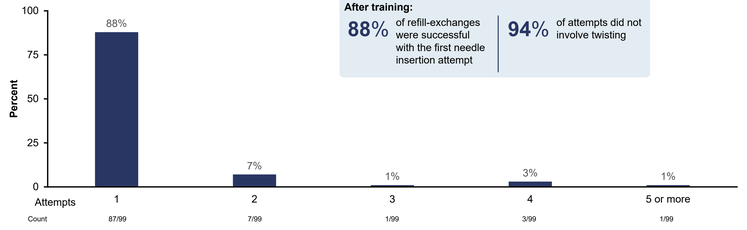
Ocular AESI n (%)	Ladder EOS ALL PDS PRN (n = 179)	Archway EOS PDS 100 mg/mL Q24W (n = 248)	Pagoda PA PDS 100 mg/mL Q24W (n = 326)	Pavilion PA PDS 100 mg/mL Q36W (n = 105)
	Pre 2016 IFU update 11/22 (50.0) Post 2016 IFU update 8/157 (5.1)			
Vitreous haemorrhage	4 (1.6)	15 (6.0)	31 (9.7)	6 (5.7)
Implant dislocations	0	10 (4.0)	6 (1.9)	1 (1.0)
Conjunctival erosion	5 (2.8)	6 (2.4)	4 (1.3)	2 (1.9)
Conjunctival retraction	3 (1.7)	4 (1.6)	0	0
Endophthalmitis	3 (1.7)			

Ladder clinical trial [NCT02510794]. Archway clinical trial [NCT03677934]. Pagoda clinical trial [NCT04108156]. Pavilion clinical trial [NCT04503551]. AE, adverse event; AESI, adverse event of special interest; DMO, diabetic macular oedema; DR, diabetic retinopathy; EOS, end of study; IFU, Instructions for Use; nAMD, neovascular age-related macular degeneration; PA, primary analysis; PDS, Port Delivery System with ranibizumab; PRN, pro re nata; Q24W, every 24 weeks; Q36W, every 36 weeks.

Training Improves Refill-Exchange Success Rate

99 videos from Pagoda, Pavilion and Portal of 20 surgeons who had completed training were reviewed

Number of Refill Needle Insertion Attempts Required for Refill



After training:

88% of refill-exchanges were successful with the first needle insertion attempt

94% of attempts did not involve twisting

Pagoda clinical trial [NCT04108156]. Pavilion clinical trial [NCT04503551]. Portal clinical trial [NCT03683251]. The content of this presentation does not constitute any form of training on PDS or any associated surgical procedures. In addition, the content of this presentation is not a substitute for training on PDS or any associated surgical procedures. PDS, Port Delivery System with ranibizumab.

The Clinical Development Plan for the Port Delivery Platform Is Extensive, Including New Molecules Specifically Designed for Continuous Delivery

nAMD

Active	Active	Active	Active	Paused
Velodrome Phase 3b, Global	**Portal** Phase 3, Global, OLE	**Belvedere** Phase 4, US	**Burgundy** Phase 1, US	**Villa** Phase 4, Global, PASS
PDS 100 mg/mL Q24W PDS 100 mg/mL Q36W	PDS 100 mg/mL Q24W or Q36W	PDS 100 mg/mL Q24W (prior treatment with agents other than RBZ)	Zifibancimig (Ang-2/VEGF-A DutaFab) via the PD implant or IVT injection	Non-interventional Post-Approval Safety Study

To Initiate	Active	To Initiate	Planned
Iridex Portal substudy	**COS** Portal substudy	**Hutong** Phase 3, China	**Reimplantation study**
PDS 100 mg/mL Q24W (Evaluating the safety of using the TPC laser)	PDS 100 mg/mL Q24W	PDS 100 mg/mL Q24W IVT RBZ 0.5 mg Q4W	Long-term safety follow-up of reimplanted patients

DMO and DR

Active	Active
Pagoda (DMO) Phase 3, US	**Pavilion (DR)** Phase 3, US
PDS 100 mg/mL Q24W IVT RBZ 0.5 mg Q4W	PDS 100 mg/mL Q36W Observation

nAMD and DMO

Active
TEIEN Phase 1/2, Japan
PDS 100 mg/mL Q24W

Velodrome clinical trial [NCT04657289]. Portal clinical trial [NCT03683251]. Belvedere clinical trial [NCT04853251]. Burgundy clinical trial [NCT04567303]. Pagoda clinical trial [NCT04108156]. Pavilion clinical trial [NCT04503551]. TEIEN clinical trial [JRCT2071210073]. Ang-2, angiopoietin-2; COS, clinical observation study; DMO, diabetic macular oedema; DR, diabetic retinopathy; IVT, intravitreal; nAMD, neovascular age-related macular degeneration; OLE, open-label extension; PASS, post-authorization safety study; PD, Port Delivery; PDS, Port Delivery System with ranibizumab; Q4W, every 4 weeks; Q24W, every 24 weeks; Q36W, every 36 weeks; RBZ, ranibizumab; TPC, Transscleral Photocoagulation; VEGF, vascular endothelial growth factor. Data on file. Roche/Genentech, Inc.

The PDS is the Only Continuous Drug Delivery System That Has Shown Positive Phase 3 Data Across 3 Different Indications

The **Port Delivery** implant can be used as a **platform** for **molecules designed** for **continuous delivery**[2]

PD platform

nAMD

PDS Q24W maintained vision and retinal anatomy improvements **through 5 years of follow-up[a]** in patients with **nAMD**[2]

Archway | Portal

PDS Q36W is currently under evaluation in patients with **nAMD**[3]

Velodrome

DMO

PDS Q24W resulted in robust vision and anatomical gains comparable to monthly intravitreal ranibizumab **through week 64** in patients with **DMO**[4]

Pagoda

DR

PDS Q36W resulted in **superior DRSS improvements** compared with control arm[5] and maintained vision **through week 52** in patients with **DR without DMO**[5]

Pavilion

The PDS reliably maximises visual outcomes with 1 or 2 refill-exchanges per year[2]

[a] Patients implanted with PDS during Ladder who received at least 1 study treatment of PDS 100 mg/mL and remained in Ladder/Portal ≥ 5 years. [b] Observation only, plus supplemental treatment with IVT RBZ 0.5 mg per investigator discretion. DMO, diabetic macular oedema; DR, diabetic retinopathy; DRSS, diabetic retinopathy severity score; IVT, intravitreal; nAMD, neovascular age-related macular degeneration; PD, Port Delivery; PDS, Port Delivery System with ranibizumab; Q24W, every 24 weeks; Q36W, every 36 weeks; RBZ, ranibizumab.