Interim Analysis of the Portal Extension Trial Evaluating the Long-term Safety and Efficacy of the Port Delivery System With Ranibizumab (PDS) in Neovascular Age-Related Macular Degeneration (nAMD)

Sara Haug, MD[1]; Natalia Callaway, MD[2,3]; Stephanie DeGraaf, PhD[2]; Sophie LePogam, PhD[2]; Mel Rabena, PhD[2]; Rob Smith, PhD[2]; and Giulio Barteselli, MD[2]

[1] Southwest Eye Consultants, Durango, CO; [2] Genentech, Inc., South San Francisco, CA; [3] Byers Eye Institute, Stanford University, Palo Alto, CA

381 – F0212

Purpose

- To evaluate the long-term safety and efficacy of the Port Delivery System with ranibizumab (PDS) in patients with neovascular age-related macular degeneration (nAMD)
- To describe the key steps in the PDS implant insertion and refill-exchange procedures for maximizing successful patient outcomes

Introduction

- The PDS is an innovative drug delivery system for the continuous delivery of a customized formulation of ranibizumab into the vitreous
- It is approved by the US Food and Drug Administration (FDA) for the treatment of nAMD in adults who have previously responded to ≥ 2 anti–vascular endothelial growth factor (VEGF) injections[1]
- The Portal extension trial (NCT03683251) is evaluating long-term safety and efficacy of the PDS with ranibizumab 100 mg/mL (PDS 100 mg/mL) in patients with nAMD who completed the Ladder (NCT02510794) or Archway (NCT03677934) trials, and will evaluate PDS 100 mg/mL in patients who participate in the Velodrome (NCT04657289) trial (currently enrolling)

Methods

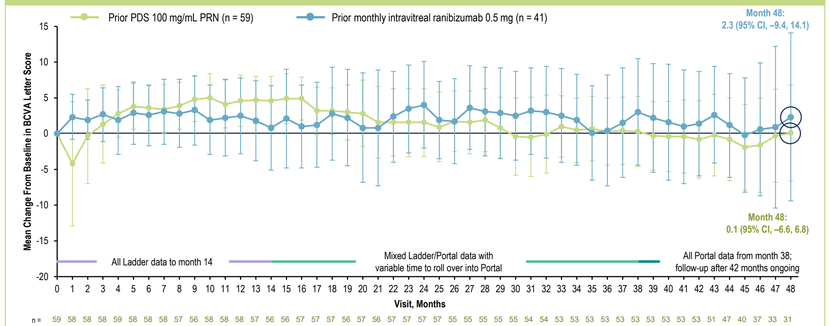
- In Ladder, patients received PDS (10, 40, or 100 mg/mL) with pro re nata (PRN) refills, or monthly intravitreal ranibizumab 0.5 mg injections (monthly ranibizumab)
- In Archway, patients received PDS 100 mg/mL with fixed refill-exchanges every 24 weeks (PDS Q24W) or monthly ranibizumab (every 4 weeks)
- Once moved to Portal, patients receive PDS Q24W from day 1
- Efficacy outcomes were assessed for Ladder-to-Portal patients treated with prior PDS 100 mg/mL PRN or prior monthly ranibizumab
- Long-term safety was analyzed using pooled data from all patients who received the PDS implant[a] in Ladder, Archway, or Portal, regardless of PDS dose (10, 40, or 100 mg/mL; all-PDS safety population), with up to ~5 years of follow-up
  - Mean (range) follow-up: 111 weeks (2.13 years [0.1–248.4 weeks])
- Please see supplementary materials for study design

[a] Via implant insertion procedure based on the Instructions for Use version published from May 2016 onward.

Conclusions

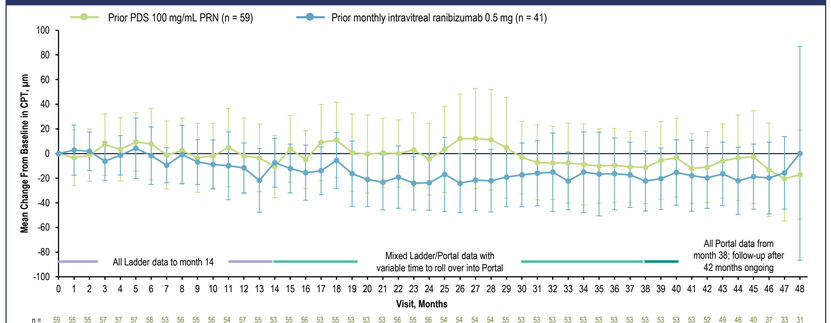
- The efficacy and safety profiles of PDS 100 mg/mL were maintained over the longer term
  - PDS 100 mg/mL demonstrated stable best-corrected visual acuity and center point thickness from Ladder baseline to Portal data cutoff (48 months from implant insertion procedure)
  - ~95% of PDS Q24W patients did not need supplemental ranibizumab treatment before each refill-exchange procedure
  - The long-term ocular safety profile of PDS is well characterized, manageable, and generally unchanged from the registration trial (Archway)
  - In PDS nAMD trials (Ladder, Archway, Portal), 2.0% of patients receiving a ranibizumab implant experienced ≥ 1 episode of endophthalmitis in data reported to March 2021[1]
- Meticulous adherence to FDA-approved surgical and refill-exchange procedures is important for optimizing patient outcomes
- 92% of patients switching from intravitreal injections in Ladder to the PDS in Portal preferred treatment with the PDS

1. Ladder to Portal: PDS Q24W Maintained Vision Through Month 48



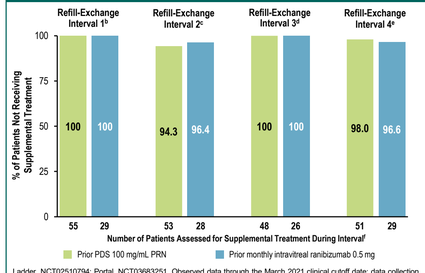
Ladder, NCT02510794; Portal, NCT03683251. Baseline is defined as the last assessment on or before the first study treatment in Ladder. Target visit dates are spaced 30 days apart for assessments in Ladder and 56 days apart for assessments in Portal. Last observation carried forward was used for intermittent missing values during Portal to correct for the difference in visit schedules. The bars represent multiplicity-adjusted 95% CIs.
BCVA, best-corrected visual acuity; PDS, Port Delivery System with ranibizumab; PRN, pro re nata; Q24W, every 24 weeks.

2. Ladder to Portal: CPT Maintained From Baseline Through Month 48



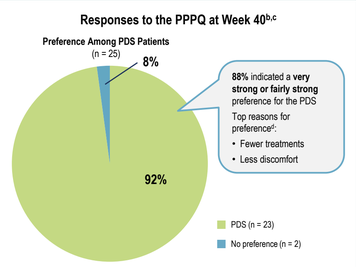
Ladder, NCT02510794; Portal, NCT03683251. Units: CFT without PED height/thickness (µm). Baseline is defined as the last assessment on or before the first study treatment in Ladder. Target visit dates are spaced 30 days apart for assessments in Ladder and 56 days apart for assessments in Portal. Last observation carried forward was used for intermittent missing values during Portal to correct for the difference in visit schedules. The bars represent multiplicity-adjusted 95% CIs.
CFT, central foveal thickness; CPT, center point thickness; PDS, Port Delivery System with ranibizumab; PED, pigment epithelial detachment; PRN, pro re nata.

3A. Ladder to Portal: Over 96 Weeks, ~95% of PDS Q24W Patients Did Not Need Supplemental Treatment Before Each Refill-Exchange Procedure[a]



Ladder, NCT02510794; Portal, NCT03683251. Observed data through the March 2021 clinical cutoff date; data collection ongoing. [a] Eligible for supplemental intravitreal ranibizumab treatment with open-label intravitreal ranibizumab if any of the following 3 criteria were met: (1) decrease of ≥ 15 letters from the best-recorded BCVA in the study; (2) increase of ≥ 150 µm in CST on SD-OCT from the lowest CST measurement in the study, or (3) increase of ≥ 100 µm in CST on SD-OCT from the lowest CST measurement in the study associated with a decrease of ≥ 10 letters from the best-recorded BCVA during the study. [b] Patients assessed at week 16. [c] Patients assessed at week 40. [d] Patients assessed at week 64. [e] Patients assessed at week 88. [f] Excludes patients who missed assessments at weeks 16, 40, 64, or 88 or who discontinued treatment early.
BCVA, best-corrected visual acuity; CST, central subfield thickness; PDS, Port Delivery System with ranibizumab; PRN, pro re nata; Q24W, every 24 weeks; SD-OCT, spectral-domain optical coherence tomography.

3B. Ladder to Portal: 92% of Patients Switching From Intravitreal Injections[a] Preferred the PDS



For patients with missing week 40 values, the last postbaseline observation was imputed. Percentages are based on total number of patients who completed the measure.
[a] On average, patients received 22 injections in Ladder before rolling over to PDS Q24W in Portal.[2] [b] The PPPQ is a 3-item questionnaire that captures a patient's preference for treatment, the strength of their preference, and the reasons for their preference. [c] Patients treated with monthly intravitreal ranibizumab 0.5 mg in Ladder who switched to PDS Q24W in Portal. [d] Results for patients with a very strong or fairly strong preference for treatment with the PDS.
PDS, Port Delivery System with ranibizumab; PPPQ, PDS Patient Preference Questionnaire; Q24W, every 24 weeks.

4. Ocular AESIs[a] Through an Average of 111 Weeks of Follow-Up (All-PDS Safety Population)

MedDRA Preferred Term[b]	All-PDS Population[c] (March 2021 CCOD; n = 555)	
	Patients With AESIs	Patients With AESIs Reported as Serious
Overall number of AESIs	**233**	**42**
Total number of patients with ≥ 1 AESI, n (%)	**137 (24.7)**	**29 (5.2)**
Endophthalmitis[d]	11 (2.0)	10 (1.8)
Implant dislocation	6 (1.1)	4 (0.7)
Vitreous hemorrhage	34 (6.1)	4 (0.7)
Rhegmatogenous retinal detachment	4 (0.7)	3 (0.5)
Conjunctival erosion	22 (4.0)	7 (1.3)
Conjunctival retraction	10 (1.8)	5 (0.9)
Conjunctival bleb/conjunctival filtering bleb leak	35 (6.3)	2 (0.4)
Hyphema	9 (1.6)	0
Cataract[e]	63 (11.4)	2 (0.4)
Septum dislodgement[f]	12 (2.2)[g]	–

There were no cases of septum dislodgement in the Portal March 2021 CCOD (presented here). In an updated analysis of safety data across all PDS trials, conducted February 2022, out of ~1195 PDS implants inserted and 4009 refill-exchange procedures, 14 cases of septum dislodgement[f] have been reported (12 cases in nAMD and 2 cases in DME[g])

Ladder, NCT02510794; Archway, NCT03677934; Portal, NCT03683251. Safety population; March 2021 CCOD. [a] Ocular AESIs potentially related to the PDS implant or implant insertion procedure. [b] Frequency counts by Preferred Term. Multiple occurrences of the same AE in an individual are counted only once for each column. [c] Includes patients originally receiving PDS 10/40 mg/mL who did not enroll in Portal and AEs for all PDS patients from time from implant insertion procedure. [d] 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] [e] Includes the following terms: cataract, cataract nuclear, cataract cortical, and cataract subcapsular. [f] Not a prespecified AESI. [g] Reported in the Pagoda trial (NCT04108156) of PDS Q24W in patients with DME.
AE, adverse event; AESI, adverse event of special interest; CCOD, clinical cutoff date; DME, diabetic macular edema; MedDRA, Medical Dictionary for Regulatory Activities; nAMD, neovascular age-related macular degeneration; PDS, Port Delivery System with ranibizumab; Q24W, every 24 weeks.

5. Implant Insertion Procedure: Meticulous Adherence to FDA-Approved Instructions for Use May Mitigate Risks Associated With the PDS

1 Case Preparation and Peritomy

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

- Conjunctival erosion/retraction
- Endophthalmitis

2 Implant Preparation

Fill implant with ranibizumab; prepare to implant

3 Scleral Dissection

Controlled 3.5-mm length cut down to pars plana

- Implant dislocation
- Conjunctival bleb

4 Laser Ablation of the Pars Plana

Endolaser probe to pretreat pars plana

- Implant dislocation
- Vitreous hemorrhage

5 Pars Plana Incision

3.2-mm stab incision through center of sclerotomy

- Vitreous hemorrhage
- Retinal detachment

6 Implant Insertion

Implant seated in incision using custom tool

7 Conjunctival and Tenon's Closure

Suture both conjunctiva and Tenon's capsule

- Conjunctival erosion/retraction
- Endophthalmitis

Risks associated with steps of the PDS implant insertion procedure if improperly done

Please see supplementary materials for standalone slide. Susvimo [Instructions for Use]. South San Francisco, CA: Genentech, Inc.; 2021.
FDA, US Food and Drug Administration; PDS, Port Delivery System with ranibizumab.

© 2022 F. Hoffmann-La Roche Ltd. All rights reserved.

6. Refill-Exchange Procedure: Meticulous Adherence to FDA-Approved Instructions for Use Is Important for Successful Outcomes

1 Patient Preparation

- Position patient: supine, ~20–30° angle
- Dilate pupil
- Apply topical anesthesia and a broad-spectrum microbicide

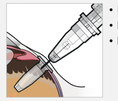
2 Syringe Preparation

- Use filter needle to withdraw ranibizumab from vial
- Replace with refill needle
- Remove air bubbles; align the plunger tip with the 0.1-mL mark
- Use within 15 minutes

3 Orient Refill Needle

- Target the center of the implant septum
- Insert the refill needle perpendicularly through the conjunctiva and into the implant septum

4 Insert Refill Needle



- Insert through conjunctiva
- Fully seat (soft stop contact)
- **Do not twist**

5 Perform Refill-Exchange

- Slowly inject (5–10 seconds)

6 Withdraw Syringe

- Withdraw syringe perpendicular to globe
- Perform indirect ophthalmoscopy

Septum dislodgement: twisting to gain access to the septum can result in damage to the overlying tissue and to the implant septum and may lead to septum dislodgement

Susvimo [Instructions for Use]. South San Francisco, CA: Genentech, Inc.; 2021.
FDA, US Food and Drug Administration; PDS, Port Delivery System with ranibizumab.

© 2022 F. Hoffmann-La Roche Ltd. All rights reserved.

Presented at the Association for Research in Vision and Ophthalmology
Denver, CO | May 1–4, 2022
Virtual | May 11–12, 2022

References

1. Susvimo [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2021.
2. Khanani AM et al; Ladder Investigators. *Ophthalmol Retina*. 2021;5(8):775-787.

Financial Disclosures

- SH: Consultant: Genentech, Inc.
- NC, SDG, SLP, MR, RS, GB: Employee: 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
- 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 Stephen Craig, PhD, CMPP, of Envision Pharma Group

Scan code to receive PDF of poster or visit https://bit.ly/35juyZc