Primary Analysis of the Phase 3 Archway Trial of the Port Delivery System With Ranibizumab (PDS) in Neovascular AMD

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Key Clinical Question

What is the safety and efficacy of the Port Delivery System with ranibizumab 100 mg/mL with fixed 24-week refill-exchanges (PDS Q24W) relative to intravitreal ranibizumab 0.5 mg injections every 4 weeks (monthly ranibizumab) in patients with neovascular age-related macular degeneration (nAMD), and how have experiences during implant insertion procedures in PDS clinical trials informed the evolution of PDS surgical methodologies?

Introduction

- The PDS is an investigational drug delivery system designed for continuous intravitreal delivery of ranibizumab
  - It comprises a permanent, refillable ocular implant filled with a customized formulation of ranibizumab
  - The implant is surgically placed at the pars plana, allowing in-clinic refill-exchange procedures
- In the Ladder phase 2 trial of the PDS for nAMD, PDS with ranibizumab 100 mg/mL demonstrated visual and anatomic outcomes comparable with monthly intravitreal ranibizumab 0.5 mg injections, was generally well tolerated, and supported evaluation in the Archway phase 3 trial[1]
- Archway is an ongoing phase 3 trial evaluating the safety and efficacy of the PDS Q24W compared with monthly ranibizumab in patients with nAMD

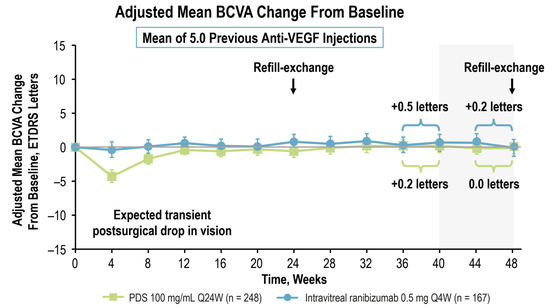
Methods

- Archway (NCT03677934) is an ongoing, phase 3, randomized, active comparator–controlled trial
- Patients were diagnosed within 9 months of screening and were responsive to anti–vascular endothelial growth factor therapy
- Randomization was 3:2 PDS Q24W to monthly ranibizumab
- Archway evaluated noninferiority and equivalence of the PDS Q24W versus monthly ranibizumab
- The primary endpoint was change in best-corrected visual acuity (BCVA) score from baseline averaged over weeks 36 and 40
- The September 2020 data cut extended efficacy results through ≥ 48 weeks of follow-up, covering 2 complete refill-exchange intervals for PDS patients
- Collective experiences during the implant insertion procedures in PDS clinical trials have informed the evolution of PDS surgical methodologies, with the goal of optimizing surgical outcomes

Conclusions

- Primary endpoint: PDS Q24W was noninferior and equivalent for BCVA change at the average of weeks 36 and 40
- BCVA change at the average of weeks 44 and 48 remained noninferior through 2 refill-exchange intervals
- Observed vision and anatomic results were comparable with monthly ranibizumab through week 48
- > 90% of patients did not receive supplemental treatment through week 48
- The PDS surgery-device-drug combination was generally well tolerated
- The PDS ocular safety profile was generally unchanged from the primary analysis
- The optimized implant insertion procedures support successful patient outcomes, including:
  - Edge-to-edge laser ablation of the pars plana to ensure postoperative hemostasis
  - Careful management of both the conjunctiva and Tenon's capsule to preserve tissue integrity
  - Precise 3.2-mm pars plana incision to reduce the risk of postoperative vitreous hemorrhage
- Standardized surgical training and ongoing procedural evaluations for enhancing surgeon proficiency

1. PDS Q24W Was Noninferior and Equivalent to Monthly Ranibizumab at the Average of Weeks 36 and 40 (Primary Endpoint) and Noninferior[a] at the Average of Weeks 44 and 48



Primary endpoint:

Change in BCVA from baseline averaged over weeks 36 and 40

Difference in adjusted means (95% CI)

–0.3 (–1.7, +1.1)

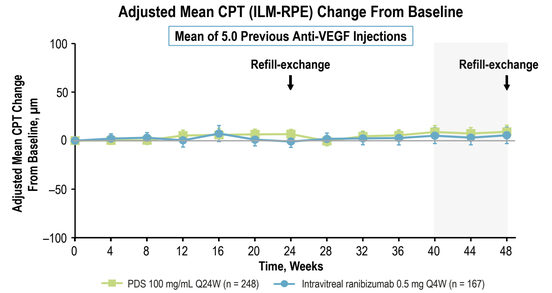
Change in BCVA from baseline averaged over weeks 44 and 48

Difference in adjusted means (95% CI)

–0.2 (–1.8, +1.3)

Adjusted means from a mixed-effect model for repeated measures (MMRM) analysis through week 48. Vertical bars represent 95% CI. 95% CI is a rounding of 95.03% CI; the type 1 error was adjusted for interim safety monitoring. Adjusted means estimated using a MMRM with adjustment for change from baseline in BCVA as the response and included terms for treatment group, visit, treatment-by-visit interaction, and baseline BCVA (< 74 ETDRS letters vs ≥ 74 ETDRS letters). [a] Equivalence not assessed at weeks 44 and 48 per protocol. BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; PDS, Port Delivery System with ranibizumab; Q4W, every 4 weeks; Q24W, every 24 weeks; VEGF, vascular endothelial growth factor.

2. Adjusted Mean CPT: PDS Q24W and Monthly Ranibizumab Results Were Comparable Through Weeks 40 and 48

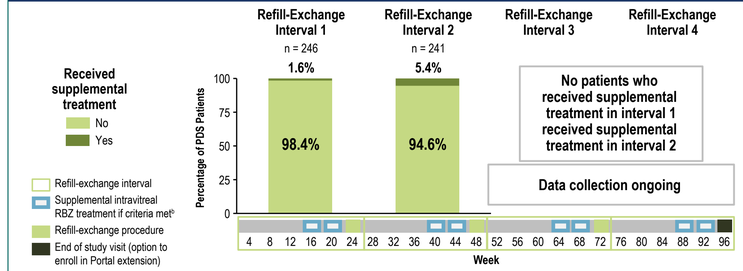


Week 36 Change From Baseline (Secondary Endpoint)
+5.4 µm
+2.6 µm
Difference in adjusted means (95% CI): +2.8 (–6.2, +11.9)

Week 48 Change From Baseline
+9.1 µm
+5.5 µm

CPT defined as retinal thickness in the center of the fovea measured between the ILM and the inner third of the RPE layer. Adjusted means from a mixed-effect model for repeated measures (MMRM) analysis through week 40. MMRM adjustment for change from baseline in CPT score as the response and included terms for treatment group, visit, treatment-by-visit interaction, and baseline best-corrected visual acuity (< 74 Early Treatment Diabetic Retinopathy Study [ETDRS] letters vs ≥ 74 ETDRS letters). Vertical bars represent 95% CI. 95% CI is a rounding of 95.03% CI; the type 1 error was adjusted for interim safety monitoring. CPT, center point thickness; ILM, internal limiting membrane; PDS, Port Delivery System with ranibizumab; Q4W, every 4 weeks; Q24W, every 24 weeks; RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.

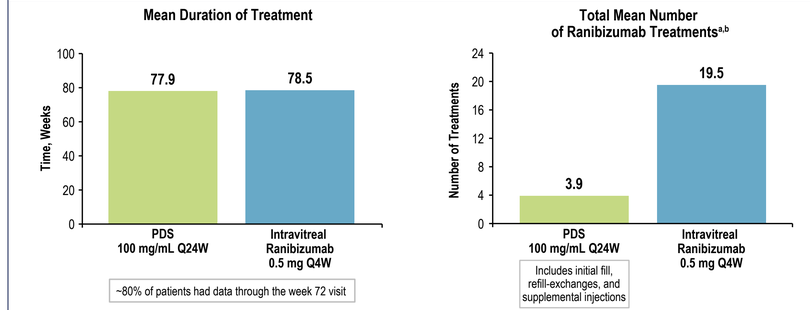
3. > 90% of PDS Patients Did Not Receive Supplemental Treatment Before Each Refill-Exchange Procedure[a]



- Supplemental intravitreal ranibizumab treatment criteria were based on BCVA and CST changes due to nAMD disease activity
- CST was measured on SD-OCT from ILM-Bruch's and included PED height if present

For each interval, percentages of patients who did/did not receive supplemental treatment were calculated out of the number of patients who were on treatment and assessed for supplemental treatment for ≥ 1 visit (interval 1, week 16 or 20; interval 2, week 40 or 44). [a] Percentage of patients receiving/not receiving treatment at each interval is calculated separately (not cumulative). [b] Eligible for supplemental intravitreal ranibizumab treatment with open-label intravitreal ranibizumab if any of the 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; (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. BCVA, best-corrected visual acuity; CST, central subfield thickness; ILM, internal limiting membrane; nAMD, neovascular age-related macular degeneration; PDS, Port Delivery System with ranibizumab; PED, pigment epithelial detachment; RBZ, ranibizumab; SD-OCT, spectral-domain optical coherence tomography.

4. Number of Treatments in PDS Q24W Patients Over a Mean Duration of 78 Weeks



Data through the September 11, 2020 clinical cutoff date; data collection ongoing. [a] Total number of ranibizumab treatments includes initial fill, refill-exchanges, and supplemental intravitreal ranibizumab 0.5 mg injections in PDS-treated patients and all intravitreal ranibizumab 0.5 mg injections in patients in the intravitreal ranibizumab 0.5 mg Q4W arm. [b] Includes PDS patients who received supplemental treatment. PDS, Port Delivery System with ranibizumab; Q4W, every 4 weeks; Q24W, every 24 weeks.

5. Ocular AESIs[a] Through an Average of 79 Weeks of Follow-up

PDS implant insertion and refill-exchange procedures were generally well tolerated

	PDS 100 mg/mL Q24W (n = 248)		Intravitreal Ranibizumab 0.5 mg Q4W (n = 167)	
MedDRA Preferred Term, n (%)[b]	Onset After Week 40	Overall[c]	Onset After Week 40	Overall[c]
Overall number of AESIs	20	87	5	15
Patients with ≥ 1 ocular AESI	13 (5.2%)	55 (22.2%)	5 (3.0%)	15 (9.0%)
Cataract[d]	11 (4.4%)	20 (8.1%)	2 (1.2%)	8 (4.8%)
Conjunctival bleb/conjunctival filtering bleb leak	1 (0.4%)	17 (6.9%)	0	0
Conjunctival erosion	1 (0.4%)	6 (2.4%)	0	0
Conjunctival retraction	0	5 (2.0%)	0	0
Endophthalmitis	1 (0.4%)	4 (1.6%)	1 (0.6%)	1 (0.6%)
Hyphema	0	1 (0.4%)	0	0
Rhegmatogenous retinal detachment	0	2 (0.8%)	0	0
Tractional retinal detachment	0	0	0	0
Vitreous hemorrhage	2 (0.8%)	15 (6.0%)	2 (1.2%)	6 (3.6%)

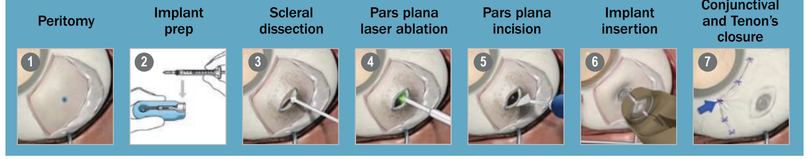
- 3 PDS patients experienced implant dislocation; 2 had onset after week 40
- 1 of 248 PDS-treated patients had irreversible vision loss due to an adverse event (*E. faecalis* endophthalmitis); no new events after week 40
- Systemic safety of PDS Q24W was generally comparable with monthly ranibizumab

Observed data, all treated patients who received ≥ 1 dose of study drug according to the actual treatment. [a] Protocol-defined ocular AESIs potentially related to the PDS implant or implant insertion procedure. [b] Frequency counts by Preferred Term. Multiple occurrences of the same adverse event in an individual are counted only once for each column. [c] All data through the September 11, 2020 clinical cutoff date. [d] Includes the following terms: cataract, cataract nuclear, cataract cortical, cataract subcapsular. AESI, adverse event of special interest; MedDRA, Medical Dictionary for Regulatory Activities; PDS, Port Delivery System with ranibizumab; Q4W, every 4 weeks; Q24W, every 24 weeks.

6. The PDS Surgical Procedures Have Evolved to Support Optimal Outcomes

Following all surgical steps as prescribed in the Instructions for Use is required to maximize optimal surgical outcomes

Critical Steps for Surgical Success



Control of hemostasis is critical at all steps, but especially at steps 1, 3, 4, and 5, to ensure optimal visualization and minimize risk of postoperative vitreous hemorrhage

PDS, Port Delivery System with ranibizumab.

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References

1. Campochiaro PA et al. *Ophthalmology*. 2019;126(8):1141-1154.

Financial Disclosures

- DE: Investigator: Alkahest, AsclepiX, Chengdu Kanghong, Gemini, Ionis, Mylan, NGM, Ophthotech, Opthea; Consultant, Investigator, Speaker: Allergan, Genentech, Inc., Novartis; Consultant, Investigator: Alimera, Gyroscope, Iveric Bio, Kodiak, Regeneron; Consultant, Investigator, Equity: Clearside; Equity: Boston Image Reading Center, Hemera, US Retina; Consultant: Apellis, KKR, Notal Vision, Recens Medical; Consultant, Speaker: DORC, EyePoint; Equity, Founder: Network Eye
- NS, DKaufman, DKardatzke, SP, SG, GB: Employee, Salary: Genentech, Inc.
- JC: Employee, Salary: F. Hoffmann-La Roche Ltd.

Study Disclosures

- This study includes research conducted on human subjects
- Institutional Review Board approval was obtained prior to study initiation
- Genentech, Inc. participated in the study design, conducting the study, and data collection, management, and interpretation
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