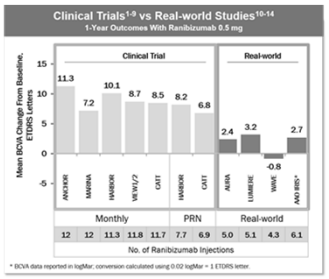
Ladder Trial of the Port Delivery System With Ranibizumab: Initial Study Results

Port Delivery System with ranibizumab

Ladder

Real-world Visual Acuity Outcomes Fall Short of Clinical Trial Results

- Frequent monitoring and injections impose a significant burden on patients, caregivers, and physicians
- Need a solution to reduce treatment burden and improve real-world patient outcomes

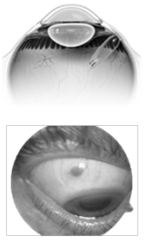


1. Brown DM et al. N Engl J Med. 2006;355:1432-1444. 2. Brown DM et al. Ophthalmology. 2009;116(1):57-65.e5. 3. Busbee BM et al. Ophthalmology. 2013;120(5):1046-1056. 4. Heier JS et al. Ophthalmology. 2012;119(12):2537-2548. 5. Ho AC et al. Ophthalmology. 2014;121(11):2181-2192. 6. Martin DF et al. Ophthalmology. 2011;118:1388-1398. 7. Martin DF et al. N Engl J Med. 2011;364:1897-1908. 8. Rosenfeld PJ et al. N Engl J Med. 2006;355:1419-1431. 9. Schmidt-Erfurth U et al. Ophthalmology. 2014;121:193-201. 10. Cohn SY et al. Retina. 2013;33:674-681. 11. Finger RP et al. Acta Ophthalmol. 2013;91:540-546. 12. Holz FG et al. Br J Ophthalmol. 2015;99:220-226. 13. Holz FG et al. Br J Ophthalmol. 2013;97:1353-1367. 14. Rao P et al. Ophthalmology. 2016;123(4):922-928. BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; PRN, as needed.

The Port Delivery System With Ranibizumab (PDS)

Enables continuous delivery of ranibizumab into the vitreous

- Innovative drug delivery system
  - Permanent, refillable intraocular Implant
  - Customized formulation of ranibizumab
  - Implant surgically placed at the pars plana
  - Refills performed in office



PDS, Port Delivery System with ranibizumab.

Ladder: A Phase 2 Randomized Active-Treatment–Controlled Clinical Trial of PDS for nAMD

Ladder: Designed to Characterize the Treatment Effect, Durability, and Safety of the PDS

Patients with nAMD responsive to anti-VEGF treatment
N = 220[a]

Randomized 2:3:3:3

Intravitreal ranibizumab 0.5 mg monthly	PDS with ranibizumab 10 mg/mL	PDS with ranibizumab 40 mg/mL	PDS with ranibizumab 100 mg/mL
n = 41	n = 58	n = 62	n = 59

Primary endpoint	Secondary endpoints		
Time to first PDS refill Assessed when last patient completed month 9 visit	Change from BL in BCVA	Change from BL in CFT	Safety

Oral antithrombotic substudy	Surgical experience of patients receiving oral antithrombotic agents

[a] Modified intent-to-treat population for efficacy analyses. 232 patients were enrolled in the trial, with 43, 63, 63, and 63 patients randomized to the intravitreal ranibizumab 0.5 monthly and PDS with ranibizumab 10 mg/mL, 40 mg/mL, and 100 mg/mL arms, respectively; 7 patients were excluded due to study site noncompliance and 5 patients were randomized but withdrew before treatment. NCT02220764. BCVA, best-corrected visual acuity; BL, baseline; CFT, central foveal thickness; nAMD, neovascular age-related macular degeneration; PDS, Port Delivery System with ranibizumab; VEGF, vascular endothelial growth factor.

Ladder Eligibility: Patients With nAMD Responsive to Prior Anti-VEGF Treatment

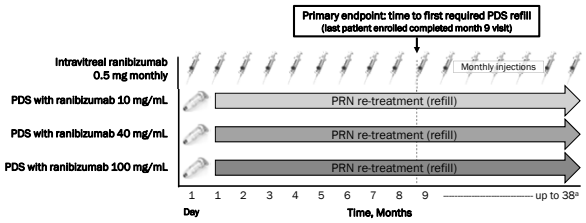
Disease
- nAMD diagnosed within 9 months of screening
- BCVA 20/20–20/200 Snellen equivalent (using ETDRS charts)

Prior treatment with anti-VEGF injections
- ≥ 2 anti-VEGF injections before screening
- Ranibizumab must be most recent anti-VEGF treatment (≤ 7 days before screening)

Demonstrated response to any anti-VEGF
- Stable/improved BCVA or decreased CFT after initiation of anti-VEGF treatment

BCVA, best-corrected visual acuity; CFT, central foveal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor.

Study Design: PRN Refill of PDS vs Monthly Injections



[a] Patients could roll over into extension study.
PDS, Port Delivery System with ranibizumab; PRN, as-needed.

PDS Refill Criteria

PDS refill performed if any of the following criteria were met due to nAMD disease activity

Increase in CFT	• ≥ 75 µm compared with average of last 2 visits • ≥ 100 µm compared with lowest on-study measurement
Decrease in BCVA	• ≥ 5 ETDRS letters compared with average of last 2 visits • ≥ 10 ETDRS letters compared with best on-study measurement
Hemorrhage	• New macular hemorrhage

BCVA, best-corrected visual acuity; CFT, central foveal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; nAMD, neovascular age-related macular degeneration; PDS, Port Delivery System with ranibizumab.

Results

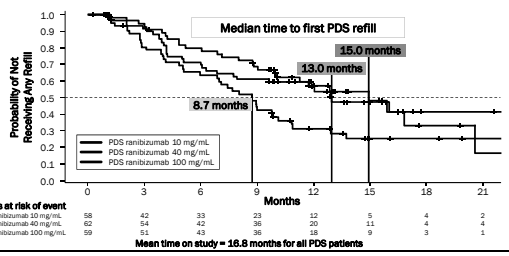
Baseline Demographics and Ocular Characteristics: Generally Well Balanced Across Treatment Arms

	Intravitreal Ranibizumab 0.5 mg Monthly (n = 41)	PDS Ranibizumab 10 mg/mL (n = 58)	PDS Ranibizumab 40 mg/mL (n = 62)	PDS Ranibizumab 100 mg/mL (n = 59)
Age, years				
Mean (SD)	71.8 (8.8)	74.3 (8.3)	74.9 (8.4)	73.4 (8.0)
Range	52–85	56–92	50–90	57–91
Sex, n (%)				
Male	13 (31.7%)	22 (37.9%)	23 (37.1%)	21 (35.6%)
BCVA, ETDRS letter score				
Mean (SD)	70.6 (12.7)	69.3 (12.8)	69.9 (11.7)	70.4 (9.8)
Snellen equivalent	20/40	20/40	20/40	20/40
Baseline CFT (ILM-Bruch's, includes PED height), µm				
Mean (SD)	280.1 (118.1)	306.8 (131.6)	297.3 (127.3)	274.7 (110.2)
Baseline CFT (ILM-RPE, excludes PED height), µm				
Mean (SD)	185.0 (61.6)	194.4 (72.6)	181.8 (73.2)	183.1 (69.2)
Time since nAMD diagnosis, months				
Mean (SD)	3.4 (1.8)	3.4 (2.0)	3.2 (1.5)	3.9 (2.1)
No. of prior anti-VEGF injections				
Mean (SD)	2.9 (1.3)	2.7 (1.2)	2.8 (1.2)	3.1 (1.5)
Range	2–7	2–7	2–6	2–8

Observed data, modified intent-to-treat population (N = 220).
BCVA, best-corrected visual acuity; CFT, central foveal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; ILM, inner limiting membrane; nAMD, neovascular age-related macular degeneration; PDS, Port Delivery System with ranibizumab; PED, pigment epithelial detachment; RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.

Primary Endpoint: Time to First Required PDS Refill

In 100 mg/mL arm, 80% of patients went ≥ 6 months without requiring a refill



No. of patients at risk of event

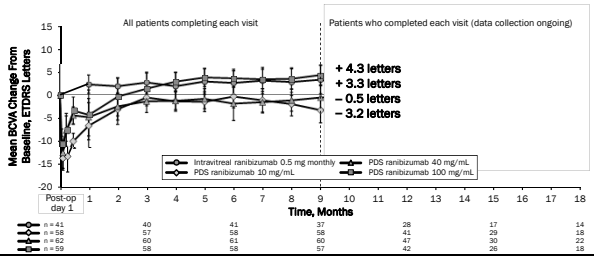
PDS with ranibizumab 10 mg/mL	58	42	33	23	12	5	4	2
PDS with ranibizumab 40 mg/mL	62	54	42	36	20	11	4	4
PDS with ranibizumab 100 mg/mL	59	51	43	36	18	9	3	1

Mean time on study = 16.8 months for all PDS patients

All PDS patients completed each visit through month 9; from month 9 on, data for patients who completed each visit (data collection ongoing). Patients censored if last visits were before cutoff date or if they discontinued the study, whichever occurred first. Time to first refill censored at the time of intravitreal injection, at the time refill criteria could not be assessed, and at the time of explant before the first refill.
PDS, Port Delivery System with ranibizumab.

Vision Outcomes at 9 Months: PDS 100 mg/mL Comparable to Monthly Intravitreal Ranibizumab Injections

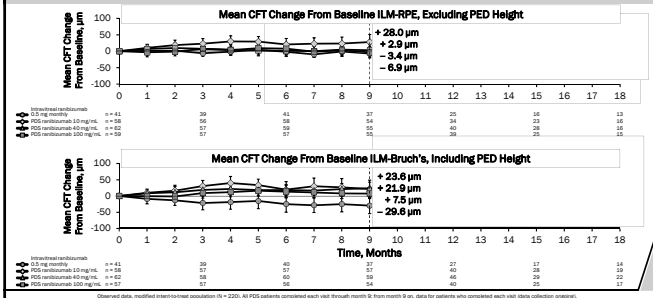
Mean BCVA Change From Baseline, Patients Previously Treated With Any Anti-VEGF[a]



n = 41	40	41	37	28	17	14
n = 58	57	58	58	41	29	18
n = 62	60	61	60	47	30	22
n = 59	58	58	57	42	26	18

[a] Patients received ≥ 2 and ≤ 9 anti-VEGF injections before baseline. Observed data, modified intent-to-treat population (N = 220). All PDS patients completed each visit through month 9; from month 9 on, data for patients who completed each visit (data collection ongoing). Vertical bars represent MCIs CI of the mean. BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; PDS, Port Delivery System with ranibizumab; post-op, post operation; VEGF, vascular endothelial growth factor.

CFT Outcomes at 9 Months: PDS Comparable to Monthly Intravitreal Injections



Observed data, modified intent-to-treat population (N = 232). All PDS patients completed each visit through month 9r from month 9 on, data for patients who completed each visit (data collection ongoing).
Vertical bars represent 95% CI of the mean.
CFT, central foveal thickness; ILM, inner limiting membrane; PDS, Port Delivery System with ranibizumab; PED, pigment epithelial detachment; RPE, retinal pigment epithelium.

Drug Release Performance Verified in Explanted Implants

- 8 Implants analyzed post-explantation
- In vitro drug release performance met specification
- 0% clogging rate

Explanted Sample	Reason for Explant	Passed In Vitro Drug Release Testing*
1	Lack of clinical efficacy	✓
2	Lack of clinical efficacy	✓
3	Lack of clinical efficacy	✓
4	Physician decision	✓
5	Adverse event	✓
6	Lack of clinical efficacy	✓
7	Lack of clinical efficacy	✓
8	Lack of clinical efficacy	✓

* Drug release rate was evaluated for explanted implants at 121 days after refill with fresh 100 mg/mL drug product. Rate based on lab evaluation of explanted implants.

PDS-Associated Events: PDS Implantation Surgery and Refill Procedure Well Tolerated by Patients

Post-op VH rate reduced significantly after modified surgical procedure implemented

	PDS Ranibizumab 10 mg/mL (n = 62)		PDS Ranibizumab 40 mg/mL (n = 63)		PDS Ranibizumab 100 mg/mL (n = 59)		Pooled PDS Arms (n = 184)	
	Time From Surgery		Time From Surgery		Time From Surgery		Time From Surgery	
MedDRA, Preferred Term, n (%)	≤ 1 Month	> 1 Month	≤ 1 Month	> 1 Month	≤ 1 Month	> 1 Month	≤ 1 Month	> 1 Month
Eye disorders								
Vitreous hemorrhage pre IFU v10	6/10 (60.0%)	0	2/7 (28.6%)	0	3/5 (60.0%)	0	11/22 (50.0%)	0
Vitreous hemorrhage post IFU v10	2/52 (3.8%)	1/52 (1.9%)	3/56 (5.4%)	1/56 (1.8%)	2/54 (3.7%)	0	7/162 (4.3%)	2/162 (1.2%)
Cataract*	0	2 (3.2%)	0	4 (6.3%)	0	8 (13.6%)	0	14 (7.6%)
Conjunctival bleb	3 (4.8%)	0	2 (3.2%)	1 (1.6%)	0	0	5 (2.7%)	1 (0.5%)
Conjunctival erosion	0	1 (1.6%)	0	2 (3.2%)	1 (1.7%)	1 (1.7%)	1 (0.5%)	4 (2.2%)
Rhegmatogenous retinal detachment	1 (1.6%)	1 (1.6%)	0	1 (1.6%)	0	1 (1.7%)	1 (0.5%)	3 (1.6%)
Tractional retinal detachment	0	1 (1.6%)	0	0	0	0	0	1 (0.5%)
Infections and infestations								
Endophthalmitis	1 (1.6%)	0	0	1 (1.6%)	0	1 (1.7%)	1 (0.5%)	2 (1.1%)
Injury, poisoning, and procedural complications								
Hyphema	4 (6.5%)	2 (3.2%)	1 (1.6%)	0	3 (5.1%)	0	8 (4.3%)	2 (1.1%)
Conjunctival retraction	0	0	1 (1.6%)	1 (1.6%)	1 (1.7%)	0	2 (1.1%)	1 (0.5%)
Conjunctival filtering bleb leak	0	0	1 (1.6%)	0	0	0	1 (0.5%)	0

IFU v10 implemented optimized surgical technique

a ≥ (7.3%) for cataract in intravitreal ranibizumab 0.5 mg monthly group when > 1 month onset and 0 when ≤ 1 month.
Observed data, all treated patients who received ≥ 1 dose of study drug according to the actual treatment. Patients from site 290667 were also included. Month 1 visit include data up to 37 days.
IFU, instructions for use; MedDRA, Medical Dictionary for Regulatory Activities; PDS, Port Delivery System with ranibizumab; post-op, post operation; VH, vitreous hemorrhage.

Systemic Safety: PDS Comparable to Monthly Ranibizumab Injections

System Organ Class Event Incidence ≥ 10%, n (%)	Intravitreal Ranibizumab 0.5 mg Monthly (n = 41)	PDS Ranibizumab 10 mg/mL (n = 58)	PDS Ranibizumab 40 mg/mL (n = 62)	PDS Ranibizumab 100 mg/mL (n = 59)
Total no. of patients with ≥ 1 AE	32 (78.0%)	44 (75.9%)	49 (79.0%)	46 (78.0%)
GI disorders	1 (2.4%)	8 (13.8%)	12 (19.4%)	13 (22.0%)
General disorders and administration site conditions	0	3 (5.2%)	5 (8.1%)	9 (15.3%)
Infections and infestations	20 (48.8%)	26 (44.8%)	26 (41.9%)	24 (40.7%)
Injury, poisoning, and procedural complications	4 (9.8%)	10 (17.2%)	11 (17.7%)	16 (27.1%)
Investigations	2 (4.9%)	5 (8.6%)	3 (4.8%)	6 (10.2%)
Metabolism and nutrition disorders	4 (9.8%)	3 (5.2%)	8 (12.9%)	5 (8.5%)
Musculoskeletal and connective tissue disorders	8 (19.5%)	8 (13.8%)	9 (14.5%)	16 (27.1%)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	4 (9.8%)	5 (8.6%)	8 (12.9%)	4 (6.8%)
Nervous system disorders	3 (7.3%)	8 (13.8%)	13 (21.0%)	18 (30.5%)
Respiratory, thoracic, and mediastinal disorders	3 (7.3%)	10 (17.2%)	10 (16.1%)	7 (11.9%)
Skin and subcutaneous tissue disorders	2 (4.9%)	1 (1.7%)	7 (11.3%)	4 (6.8%)

Observed data, safety-evaluable population who received ≥ 1 dose of study drug according to the actual treatment. Patients from site 290667 were excluded due to serious Good Clinical Practice noncompliance.
AE, adverse event; CNS, central nervous system; GI, gastrointestinal; PDS, Port Delivery System with ranibizumab.

Systemic Safety: Majority of GI, Injuries, and CNS Events in PDS Arms Were Nonserious

System Organ Class Preferred Term Incidence > 1, n (%)	Intravitreal Ranibizumab 0.5 mg Monthly (n = 41)		PDS Ranibizumab 10 mg/mL (n = 58)		PDS Ranibizumab 40 mg/mL (n = 62)		PDS Ranibizumab 100 mg/mL (n = 59)	
	Any AEs	SAEs	Any AEs	SAEs	Any AEs	SAEs	Any AEs	SAEs
Gastrointestinal disorders								
Nausea	0	0	4 (6.9%)	0	4 (6.5%)	0	4 (6.8%)	0
Constipation	0	0	3 (5.2%)	0	1 (1.6%)	0	2 (3.4%)	0
Gastroesophageal reflux disease	0	0	2 (3.4%)	0	1 (1.6%)	1 (1.6%)	3 (5.1%)	0
Diarrhea	0	0	1 (1.7%)	0	1 (1.6%)	0	2 (3.4%)	0
Toothache	1 (2.4%)	0	0	0	2 (3.2%)	0	1 (1.7%)	0
Hiatus hernia	0	0	1 (1.7%)	0	2 (3.2%)	2 (3.2%)	0	0
Injury, poisoning and procedural complications								
Fall	0	0	4 (6.9%)	0	3 (4.8%)	1 (1.6%)	4 (6.8%)	0
Contusion	1 (2.4%)	0	1 (1.7%)	0	1 (1.6%)	0	4 (6.8%)	0
Tooth fracture	1 (2.4%)	0	0	0	2 (3.2%)	0	1 (1.7%)	0
Laceration	0	0	0	0	1 (1.6%)	0	2 (3.4%)	0
Nervous system disorders								
Headache	1 (2.4%)	0	7 (12.1%)*	0	7 (11.3%)*	0	11 (18.6%)*	0
Cerebrovascular accident	0	0	0	0	2 (3.2%)	2 (3.2%)	1 (1.7%)	1 (1.7%)
Dizziness	0	0	2 (3.4%)	0	0	0	0	0
Migraine	0	0	0	0	0	0	2 (3.4%)	1 (1.7%)

*19/25 (76.0%) events of headache in the PDS arms that occurred in the peri-operative period were largely related to postoperative pain, eg, discomfort from the incision and the sutures.

Observed data, safety-evaluable population who received ≥ 1 dose of study drug according to the actual treatment. Patients from site 290667 were excluded due to serious Good Clinical Practice noncompliance.
AE, adverse event; PDS, Port Delivery System with ranibizumab; SAE, serious adverse event.

Oral Antithrombotic Substudy Results

- Performed to study surgical experience of patients receiving oral antithrombotic agents
- 11 patients on oral antithrombotic therapy received the PDS Implant
  - 4 patients were on Coumadin (warfarin); 3 interrupted drug, 1 did not
  - 5 patients were on Eliquis (apixaban, NOAC); 4 interrupted drug, 1 did not
  - 2 patients were on Pradaxa (dabigatran, NOAC); 2 interrupted drug

No vitreous hemorrhages observed in patients on oral antithrombotic therapy that underwent PDS Implant insertion surgery using optimized surgical procedure

NOAC, non-vitamin K oral anticoagulant; PDS, Port Delivery System with ranibizumab.

Conclusion

PDS Has the Potential to Reduce Intravitreal Injection Treatment Burden and Improve Real-world Clinical Outcomes

- In the PDS with ranibizumab 100 mg/mL treatment arm
  - Median time to first required refill was 15.0 months
  - 80% of patients went ≥ 6 months until the first refill
  - BCVA and anatomic outcomes comparable to those of monthly intravitreal ranibizumab
- PDS Implant insertion surgery and refill procedure were well tolerated
  - Systemic safety comparable to monthly intravitreal injections
  - Patients on oral antithrombotics able to interrupt treatment did not demonstrate an increased risk of vitreous hemorrhage
- Phase 3 program, ***Archway***, using fixed 24-week interval dosing is underway

Video: PDS Optimized Implantation Surgical Procedure