Key Learnings From the Phase 2 Ladder Trial of the Port Delivery System With Ranibizumab for Neovascular AMD

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Disclosures

- Financial disclosures
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- Study disclosures
  - This study includes research conducted on human subjects
  - Institutional Review Board approval was obtained prior to study initiation
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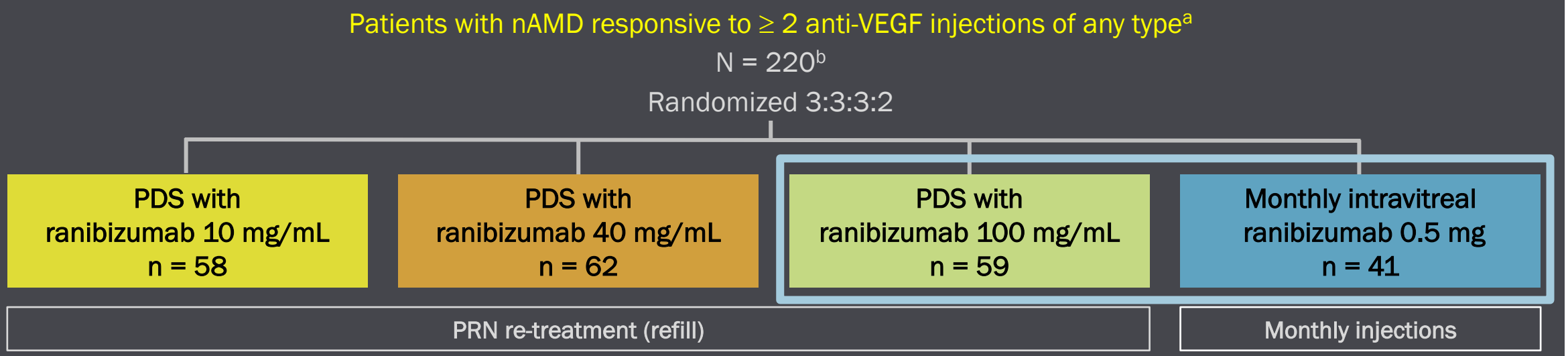
Key Takeaways
Key Learnings From the Phase 2 Ladder Trial of the PDS for nAMD

- PDS 100 mg/mL provides the efficacy and durability to support refills every 6 months
- Intentional layer-by-layer incision of the sclera until the pars plana is exposed, followed by laser ablation, is key for pars plana hemostasis
- Conjunctiva and Tenon's capsule anchorage to limbal sclera critical for maintaining coverage over implant
- The refill-exchange procedure is successfully performed with the surgeon standing on the contralateral side of the study eye, using a perpendicular approach and precise targeting

nAMD, neovascular age-related macular degeneration; PDS, Port Delivery System with ranibizumab.

Ladder Phase 2 Characterized the Treatment Effect, Durability, and Safety of the PDS

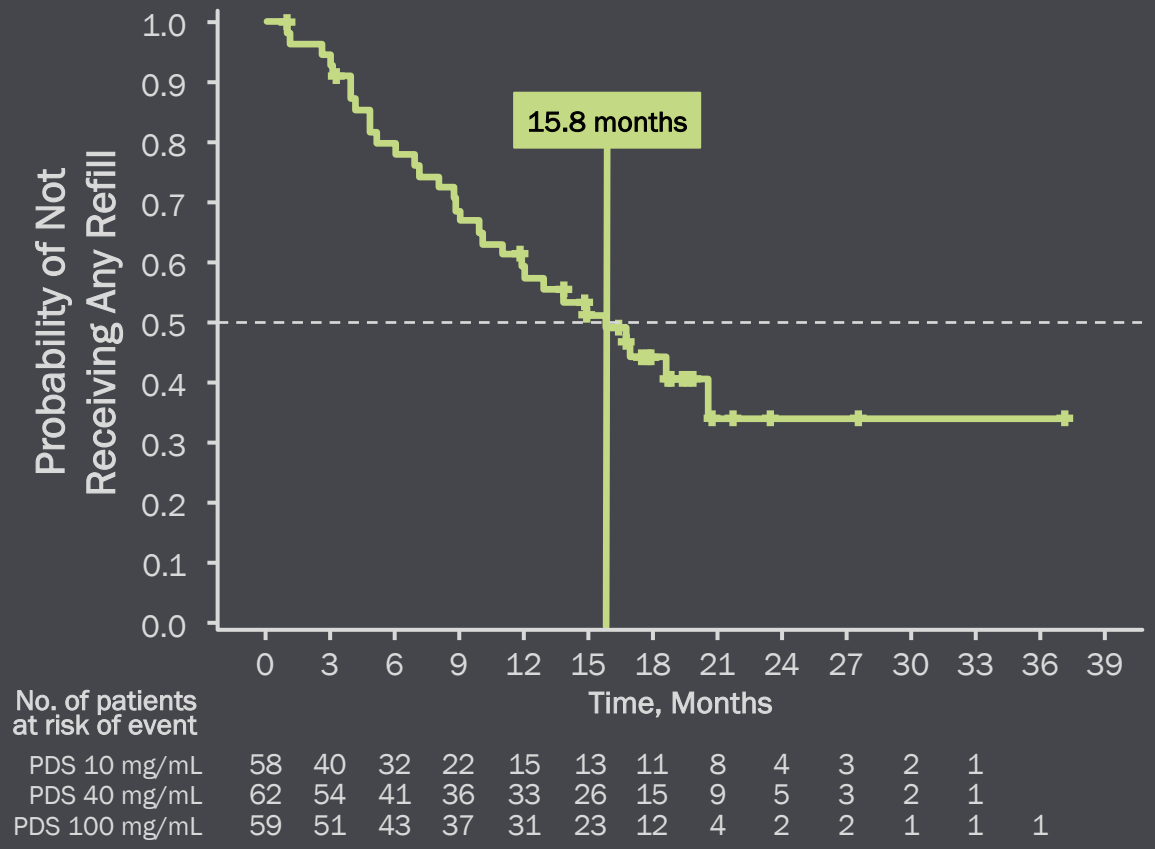


Ladder Phase 2 Trial

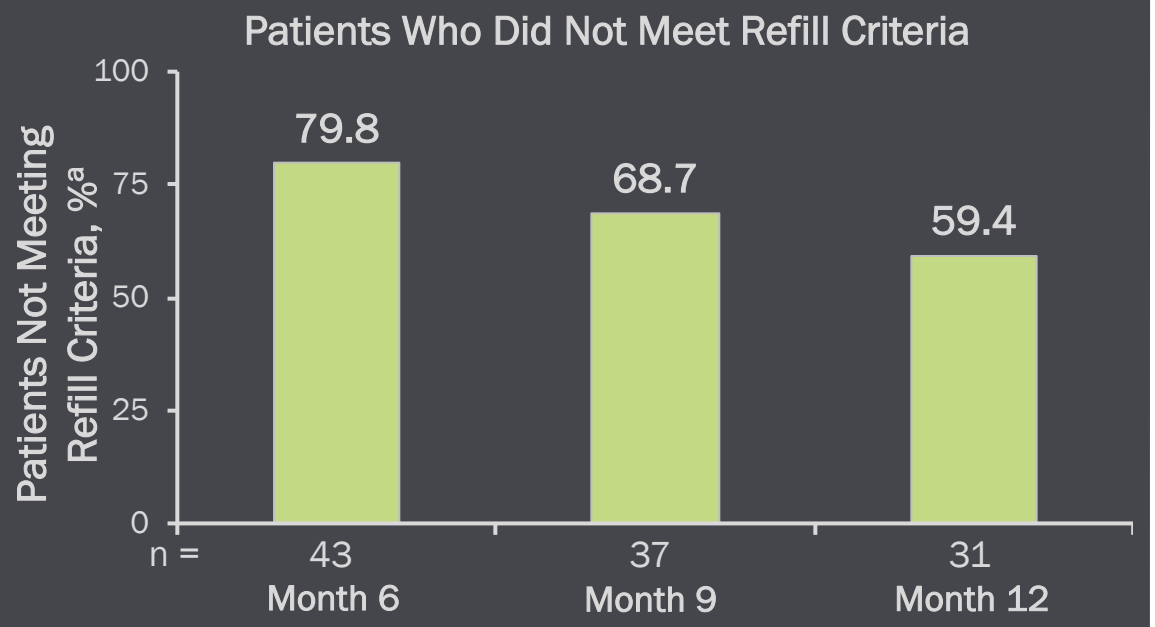
- Supported selection of PDS 100 mg/mL for phase 3
- Enabled key learnings about:
  - Treatment effect and durability of PDS 100 mg/mL
  - PK profile of PDS 100 mg/mL
  - Techniques of PDS implantation and refill-exchange procedures

[a] ≥ 2 anti-VEGF injections before screening to determine responsiveness; ranibizumab must be most recent anti-VEGF treatment (≤ 7 days before screening). [b] Modified intent-to-treat population for efficacy analyses. 232 patients were enrolled in the trial, with 63, 63, 63, and 43 patients randomized to PDS with ranibizumab 10 mg/mL, 40 mg/mL, and 100 mg/mL and monthly intravitreal ranibizumab 0.5 mg treatment arms, respectively; 7 patients were excluded due to study site noncompliance and 5 patients were randomized but withdrew before treatment. NCT02510794.
nAMD, neovascular age-related macular degeneration; PDS, Port Delivery System with ranibizumab; PK, pharmacokinetic; PRN, as-needed; VEGF, vascular endothelial growth factor.

Durability: 50% of Patients at 15.8 Months and 80% of Patients at 6 Months Did Not Require a Refill



No. of patients at risk of event													
PDS 10 mg/mL	58	40	32	22	15	13	11	8	4	3	2	1	
PDS 40 mg/mL	62	54	41	36	33	26	15	9	5	3	2	1	
PDS 100 mg/mL	59	51	43	37	31	23	12	4	2	2	1	1	1

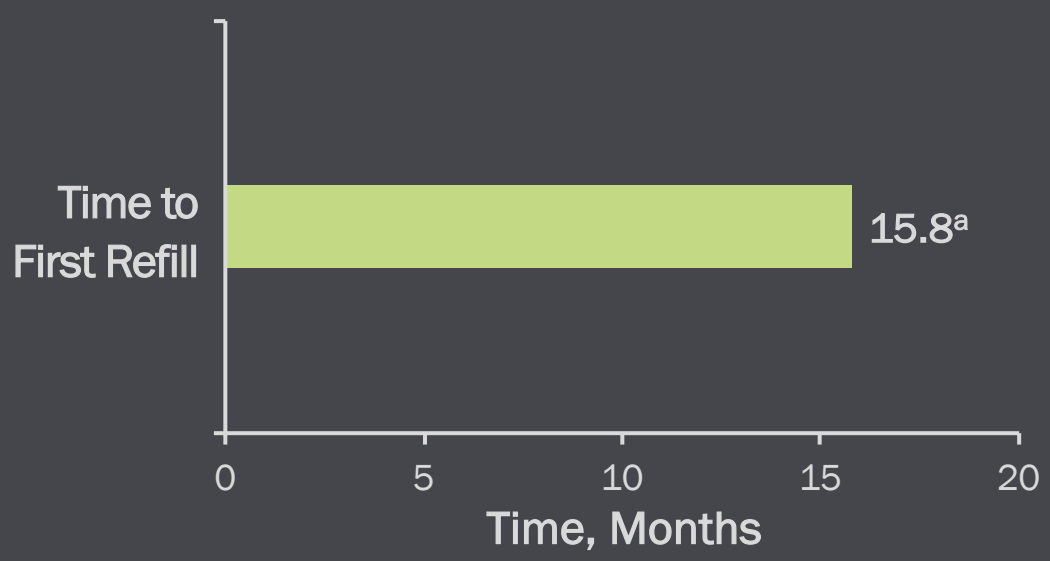


[a] Kaplan-Meier estimate of time to first refill. Censoring date defined as the date of a patient's last visit before the cutoff date or the date they discontinued the study, whichever occurred first. Time to first refill censored at the time of intravitreal injection, at the time refill criteria could not be assessed, and at the time of explant before the first refill.
PDS, Port Delivery System with ranibizumab.

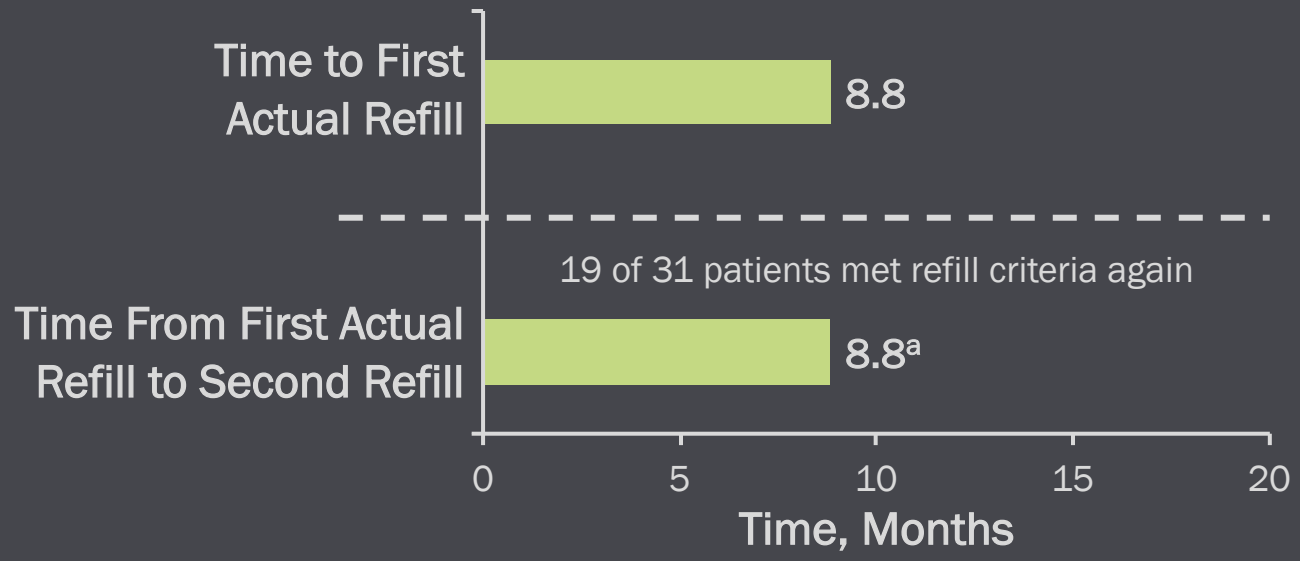
Consistency in Refills

Median Time of 8.8 Months to First and Second Refills in Patients Needing Refills

All PDS 100 mg/mL Patients
59 patients



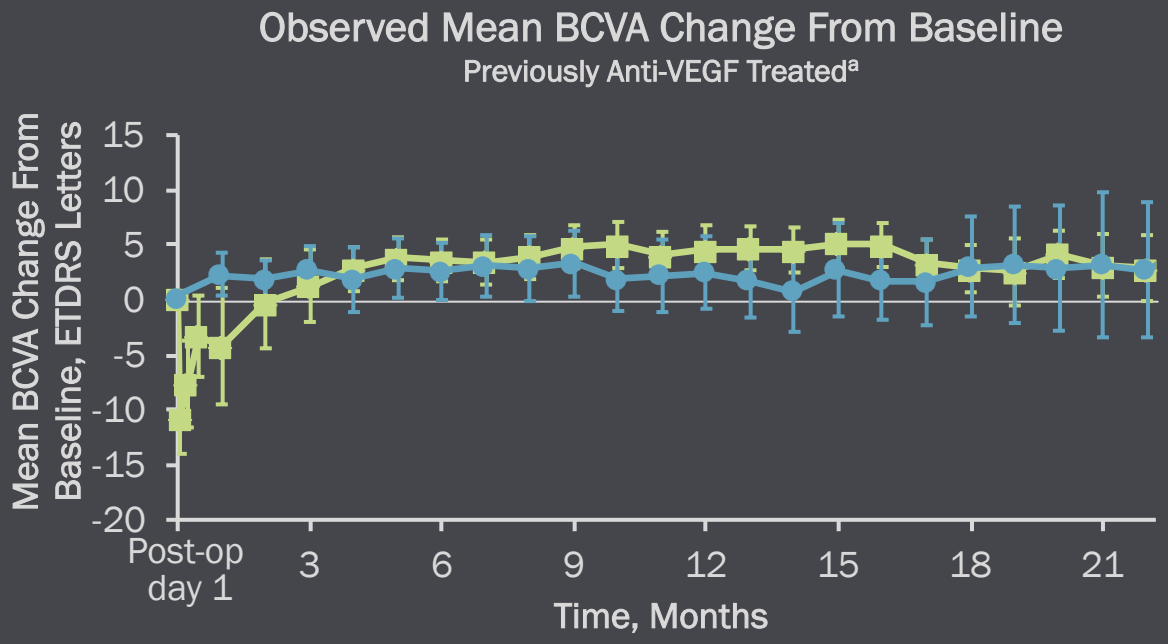
PDS 100 mg/mL Patients With ≥ 1 Actual Refill
31 patients

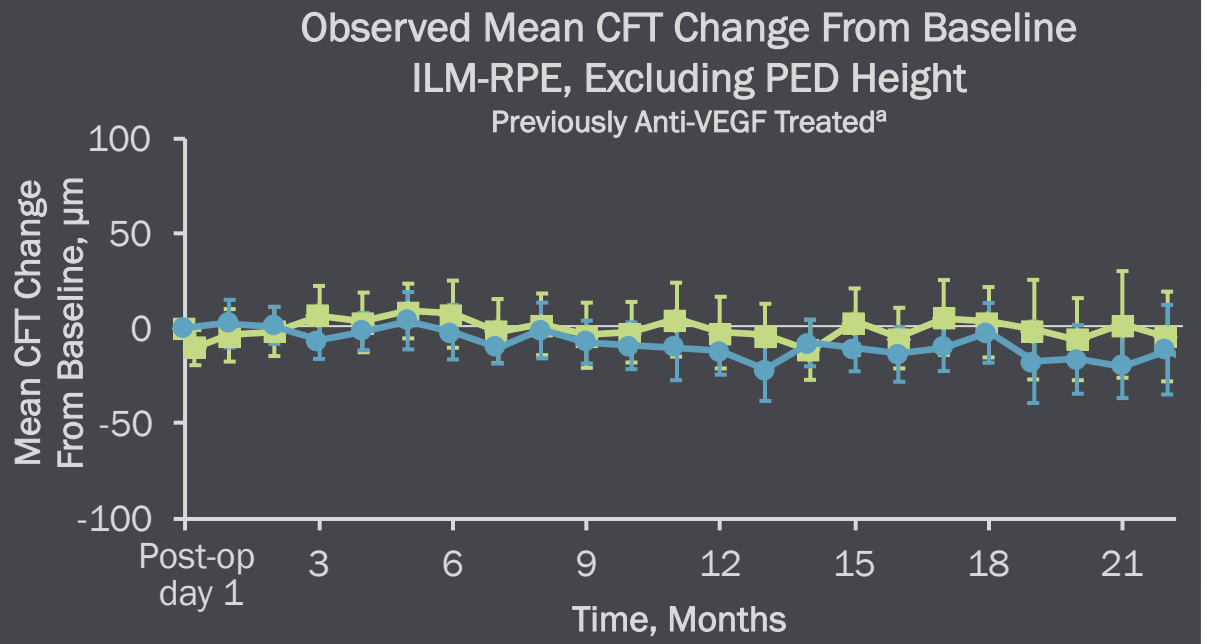


[a] Based on Kaplan-Meier estimate of median time to first refill. Time to first actual refill was defined as the time from implant insertion to the first refill-exchange procedure in the 31 patients who received a refill. The median time from first actual refill to second refill was based on Kaplan-Meier estimate, with the time to first refill for the 12 patients who did not meet refill criteria a second time being censored at the time of study exit.
PDS, Port Delivery System with ranibizumab.

BCVA and CFT Outcomes Similar Between PDS 100 mg/mL and Monthly Ranibizumab Over a Mean 22 Months

Mean time on study = 22.1 months for all PDS patients (range, 10.8–37.6 months)





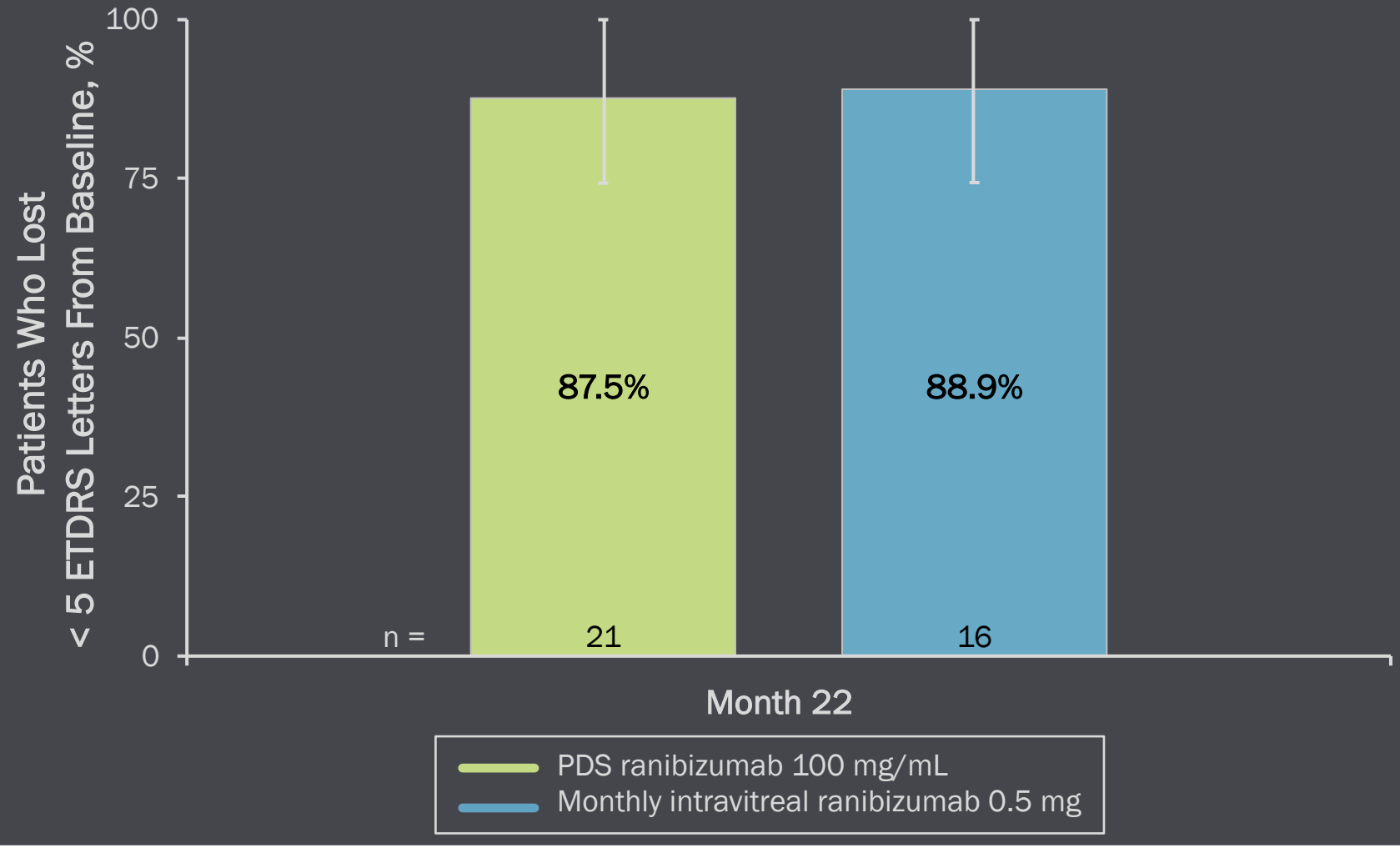
PDS ranibizumab 100 mg/mL
Monthly intravitreal ranibizumab 0.5 mg

[a] Patients received ≥ 2 and ≤ 9 of any anti-VEGF injection before baseline. Observed data, modified intent-to-treat population (N = 220). Data for patients who completed each visit. Vertical bars represent 95% CI of the mean.

BCVA, best-corrected visual acuity; CFT, central foveal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; ILM, inner limiting membrane; PDS, Port Delivery System with ranibizumab; PED, pigment epithelial detachment; post-op, post operation; RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.

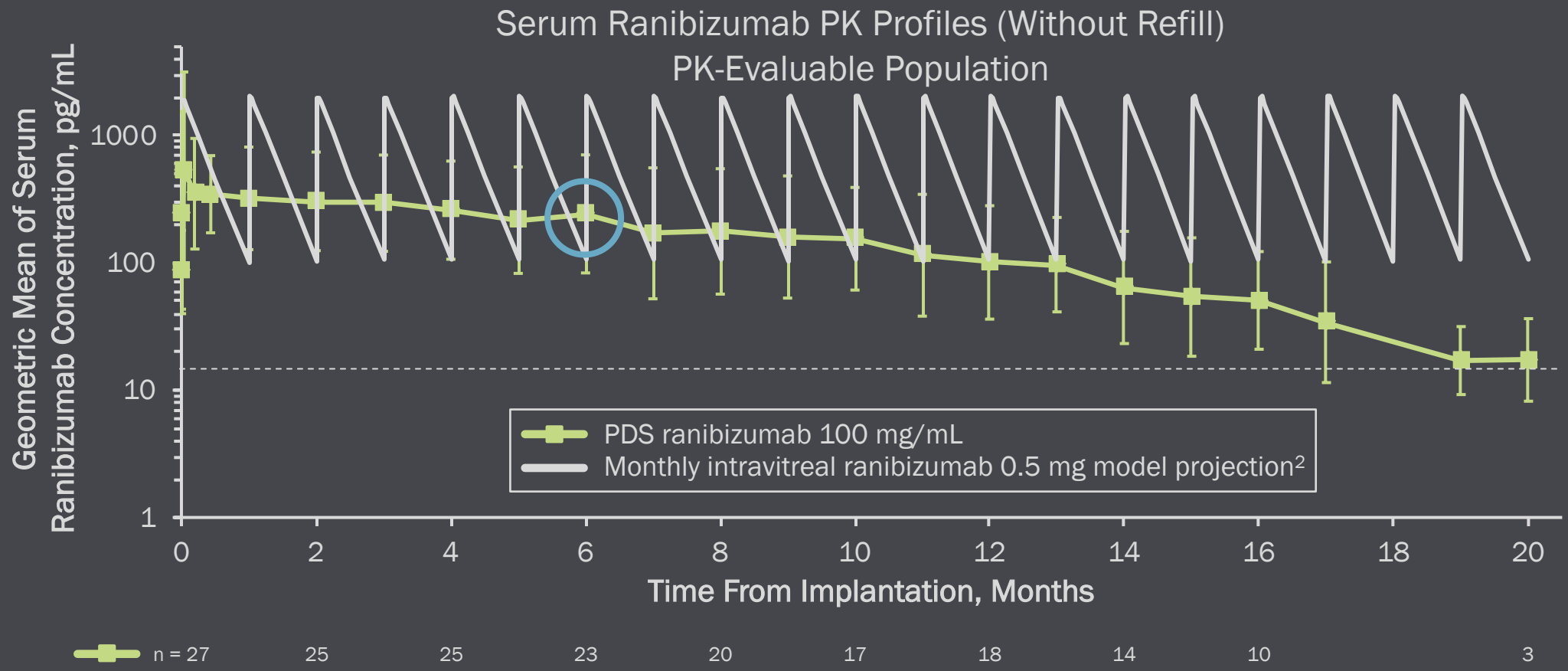
Robust Maintenance of BCVA Over a Mean 22 Months on Study

PDS 100 mg/mL Comparable With Monthly Ranibizumab Injections



Observed data, modified intent-to-treat population (N = 220). Data for patients who completed each visit. Vertical bars represent 95% CI of the mean.
BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; PDS, Port Delivery System with ranibizumab.

In PDS 100 mg/mL, the Implant Continues to Release Ranibizumab Through At Least Month 16



Analysis excludes patients who had received intravitreal ranibizumab injections in the fellow eye, received supplemental intravitreal ranibizumab injections, or received prior intravitreal injections with bevacizumab. Patient numbers decreased over time as patients got refills. For a given arm and sampling time point, if more than one-third of values were below the lower limit of quantification, no value is reported.

Vertical bars represent the geometric mean */÷ geometric SD.

1. Lowe J et al. *J Immunol Methods*. 2018;461:44-52. 2. Xu L et al. *Invest Ophthalmol Vis Sci.* 2013;54(3):1616-1624.

PDS, Port Delivery System with ranibizumab; PK, pharmacokinetic.

Scleral Dissection Followed by Laser Ablation of the Pars Plana Key for Achieving Postoperative Hemostasis

Scleral Dissection

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Laser Ablation of Pars Plana

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Postoperative vitreous hemorrhage rate was reduced from 50.0% to 3.8% after optimization of the surgical procedure[a]

[a] Ladder postoperative vitreous hemorrhage results from end of study analysis. Results are for events that occurred up to day 37 post implant insertion.

1. Bantseev V et al. *Retina* [published online August 19, 2019]. doi: 10.1097/IAE.0000000000002614.

Conjunctiva and Tenon's Dissection at Peritomy and Anchorage of Both Layers to Limbus During Closure Are Crucial for Optimal Surgery Outcomes

Peritomy[a]

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Crucial Steps in Peritomy

- Identify, preserve Tenon's capsule
- Blunt dissection from limbus to fornix

Closure

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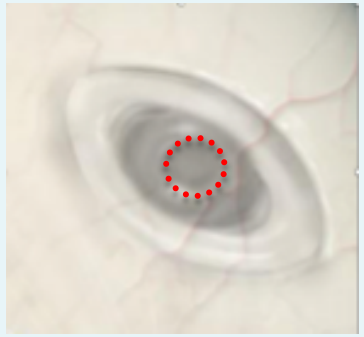
Crucial Steps in Closure

- Identify Tenon's capsule under conjunctiva
- Draw both layers across limbus over cornea
- Suture both layers at limbus with scleral bite

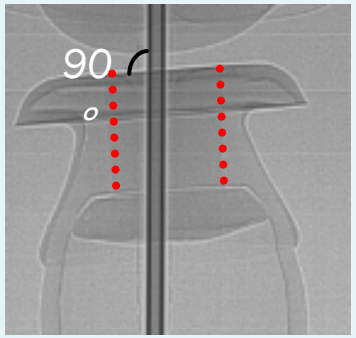
[a] Video recording from patient treated in Archway.

Refill-Exchange Procedure Requires a Perpendicular Approach and Precise Targeting

Targeting



Perpendicularity



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Ladder Phase 2 Trial Key Learnings

- PDS 100 mg/mL provides the efficacy and durability to support refills every 6 months
- Intentional layer-by-layer incision of the sclera until the pars plana is exposed, followed by laser ablation, is key for pars plana hemostasis
- Conjunctiva and Tenon's capsule anchorage to limbal sclera critical for maintaining coverage over implant
- The refill-exchange procedure is successfully performed with the surgeon standing on the contralateral side of the study eye, using a perpendicular approach and precise targeting

In the Archway phase 3 trial, PDS 100 mg/mL Q24W achieved visual acuity outcomes equivalent to monthly ranibizumab 0.5 mg at weeks 36/40

Pagoda (DME) phase 3 trial currently enrolling

PDS has the potential to reduce treatment burden through continuous delivery of ranibizumab

Archway: NCT03677934; Pagoda: NCT04108156.
DME, diabetic macular edema; PDS, Port Delivery System with ranibizumab; Q24W, every 24 weeks.

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