Pharmacokinetic (PK) Profile of the Port Delivery System with Ranibizumab (PDS) in the Phase 2 Ladder Trial

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Port Delivery System
with ranibizumab

Disclosures

- Financial disclosures
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  - SG, MM, KM: Employee, Salary) Genentech, Inc.

- 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

PK Profile of the PDS in the Phase 2 Ladder Trial

- **Comparable:** Serum concentrations with PDS 100 mg/mL are within the range of concentrations of monthly intravitreal ranibizumab injections through at least 12 months following implantation and are measurable in serum past 16 months
- **Consistent:** Serum PK profiles are consistent following implantation and multiple refills in line with the time to first and second refills seen in Ladder

Median time to first refill of 15.8 was observed in the PDS 100 mg/mL arm.
nAMD, neovascular age-related macular degeneration; PDS, Port Delivery System with ranibizumab; PK, pharmacokinetic.

Ladder Phase 2 Trial Design

Characterize the Treatment Effect, Durability, and Safety of the PDS

Patients with nAMD responsive to ≥ 2 anti-VEGF injections of any type[a]

N = 220[b]

Randomized 3:3:3:2

PDS with ranibizumab 10 mg/mL n = 58	PDS with ranibizumab 40 mg/mL n = 62	PDS with ranibizumab 100 mg/mL n = 59	Monthly intravitreal ranibizumab 0.5 mg n = 41
PRN re-treatment (refill)			Monthly injections

Full study population (N = 220)

Provides information about exposure in full study population

PK-evaluable population (n = 68)

Provides information about PDS implant release rate

Excluded patients who received:

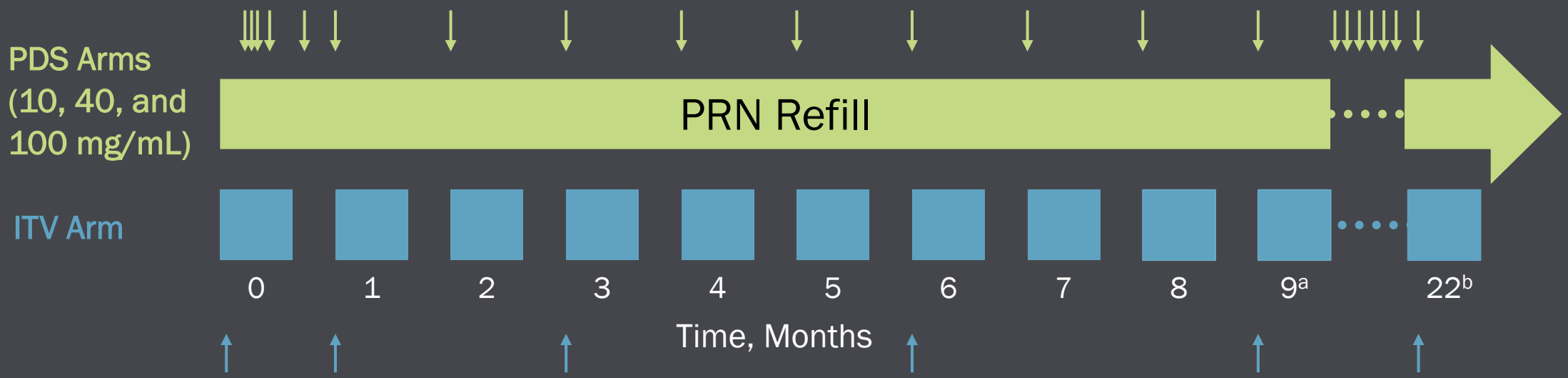
- Intravitreal ranibizumab injections in the fellow eye
- Supplemental intravitreal ranibizumab injections
- Prior intravitreal injections with bevacizumab

Mean Time on Study = 22.1 Months for All PDS Patients (Range, 10.8–37.6 Months)

[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. BCVA, best-corrected visual acuity; BL, baseline; CFT, central foveal thickness; nAMD, neovascular age-related macular degeneration; PDS, Port Delivery System with ranibizumab; PRN, as-needed; VEGF, vascular endothelial growth factor.

Serum PK Sample Collection at Predefined Time Points

Serum Ranibizumab Levels Used to Robustly Characterize PK of PDS



PRN refills of PDS

Serum sampling in PDS arms:
randomization; Day 1 ≥ 60 min following implant insertion; 1, 7, & 14 days; each monthly study visit; and 1 & 7 days after each refill

ITV RBZ 0.5 mg monthly

Serum sampling in ITV arm:
C_{trough} levels assessed at randomization; months 1, 3, 6, and 9; and final study visit

Serum concentrations were measured in all patients using a validated ELISA assay with a lower limit of quantification of 15 pg/mL[1]

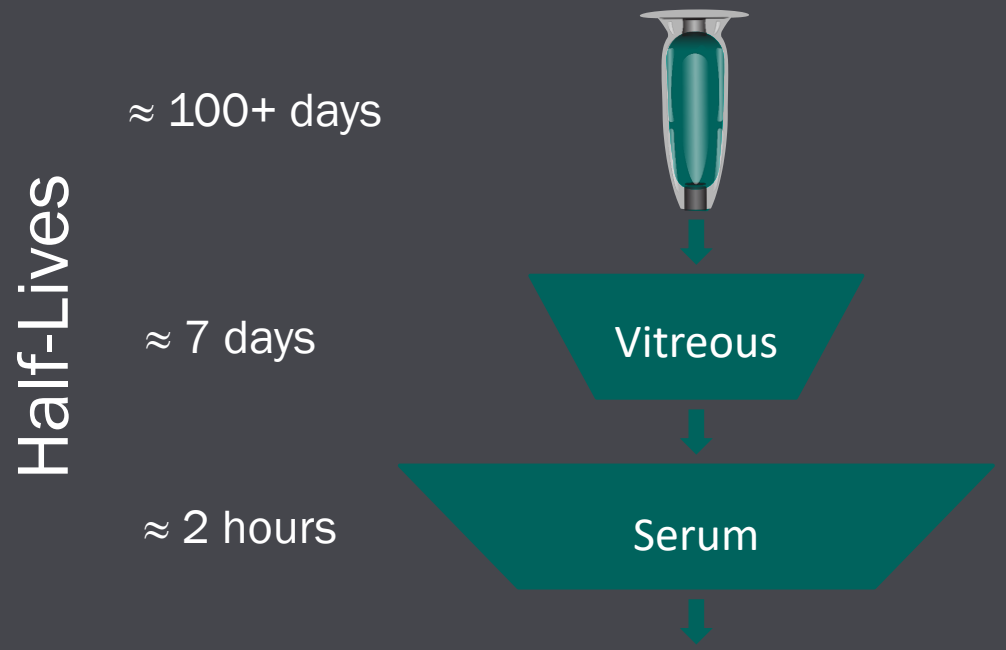
[a] Primary efficacy analysis assessed when last patient completed month 9 visit. [b] Mean time on study = 22.1 months for all PDS patients (range, 10.8–37.6 months).

1. Lowe J et al. *J Immunol Methods.* 2018;461:44-52.

C_{trough}, serum trough concentration; ELISA, enzyme-linked immunosorbent assay; ITV, intravitreal; PDS, Port Delivery System with ranibizumab; PK, pharmacokinetic; PRN, as-needed; RBZ, ranibizumab.

PDS Serum PK Profile Reflects Implant Release Rate

- Implant release is the rate-limiting step
- Implant release rate < ocular elimination rate < systemic elimination rate
- Serum PK profile is the same as implant release rate

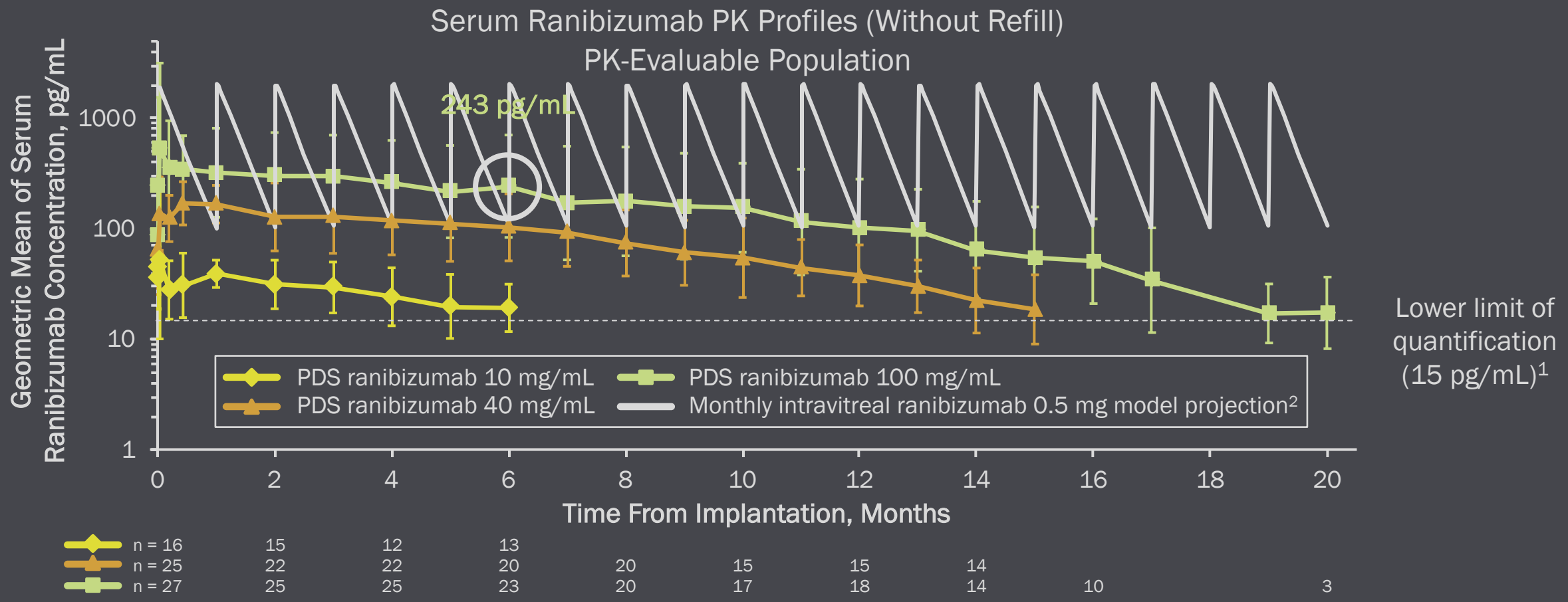


Funnel Analogy

If the funnel is large/wide but the stream flowing through it is small, a wider funnel will not increase flow. Rate will be limited by the small stream.

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

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



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.

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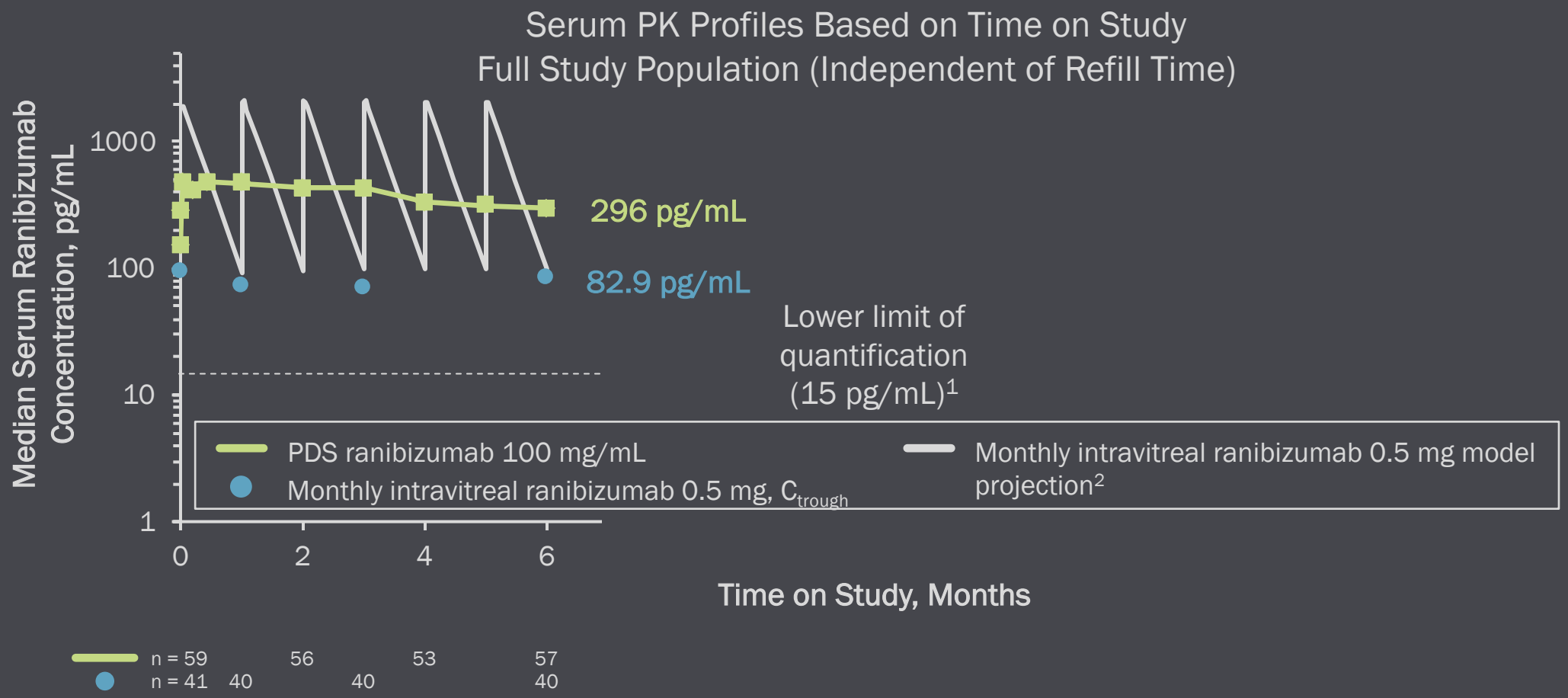
Concentrations With PDS 100 mg/mL Within the Range Seen With Monthly Intravitreal Ranibizumab Injections

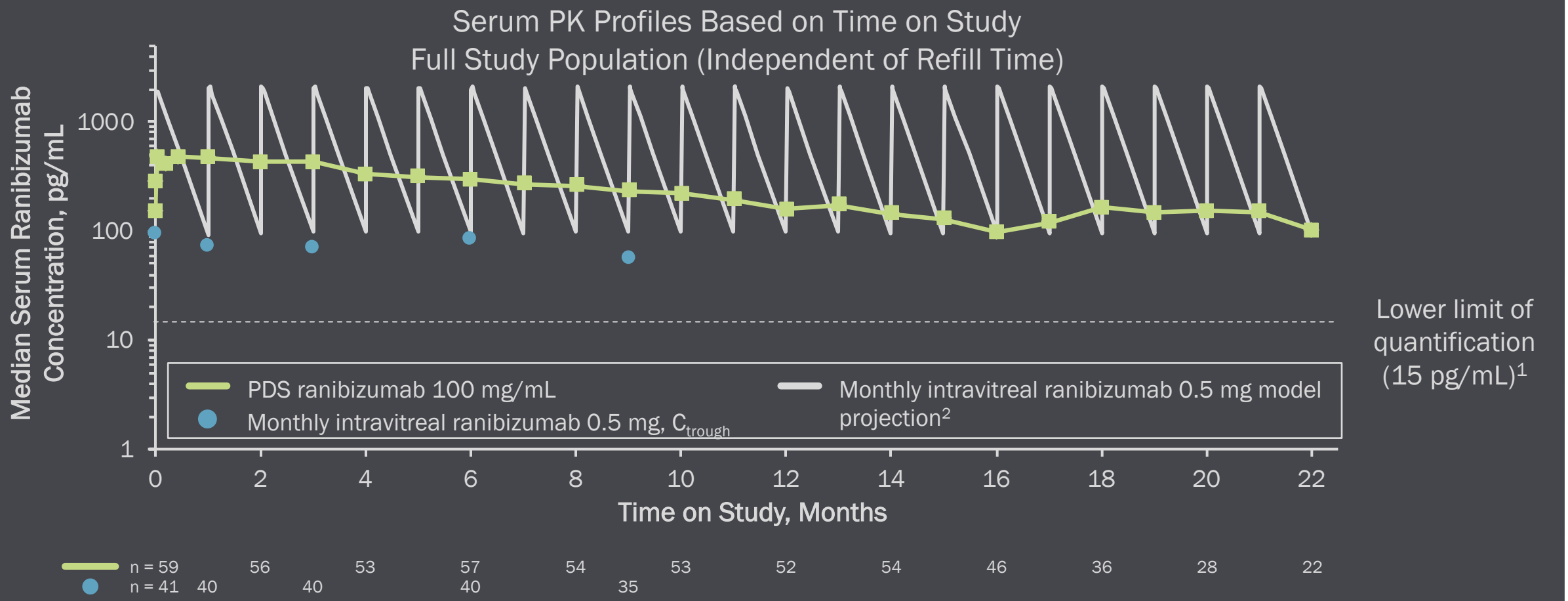


Mean Time on Study = 22.1 Months for All PDS Patients (Range, 10.8–37.6 Months)

Median (rather than geometric mean) is reported due to the variable timing of refill, and thus a log-normal distribution is not expected. Data were updated from the abstract to exclude 5 patients in the PDS 10 and 40 mg/mL arms due to study site noncompliance.

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. Figure generated based on updated population PK analysis (including data from Study FVF4579g).
C_{trough}, serum trough concentration; PDS, Port Delivery System with ranibizumab; PK, pharmacokinetic.

Concentrations With PDS 100 mg/mL Within the Range Seen With Monthly Intravitreal Ranibizumab 0.5 mg



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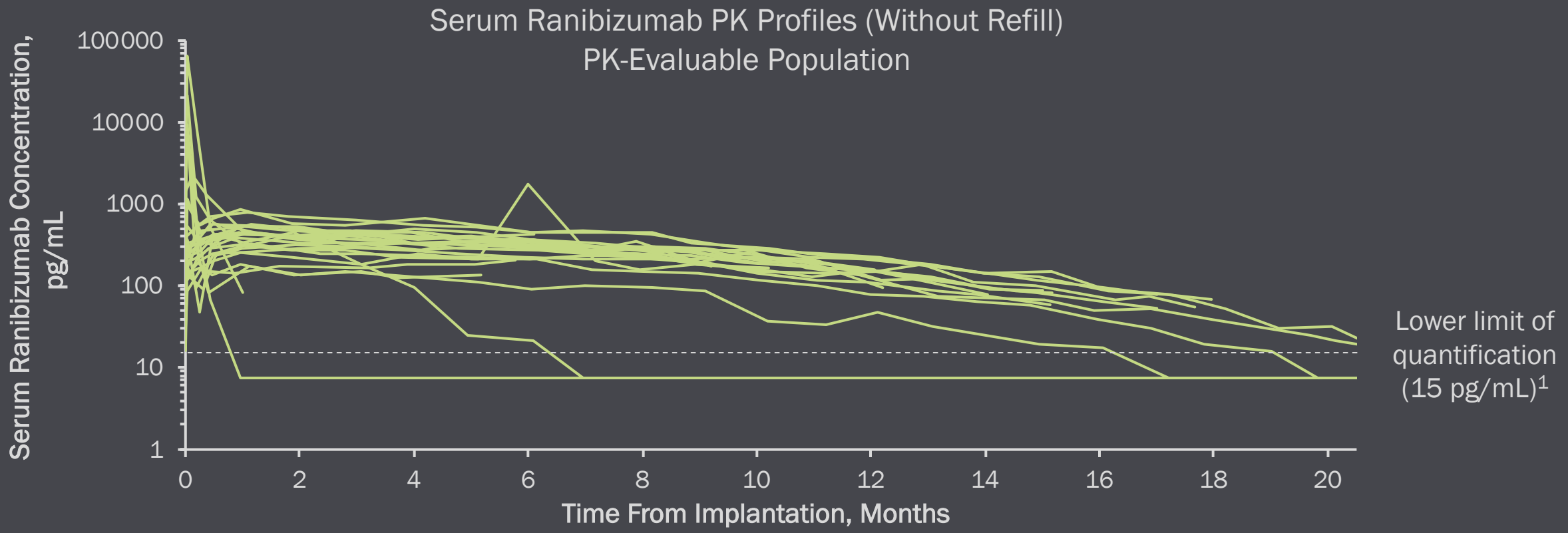
PDS Continuously Delivers Ranibizumab for Extended Durations Consistently Across PDS 100 mg/mL Patients



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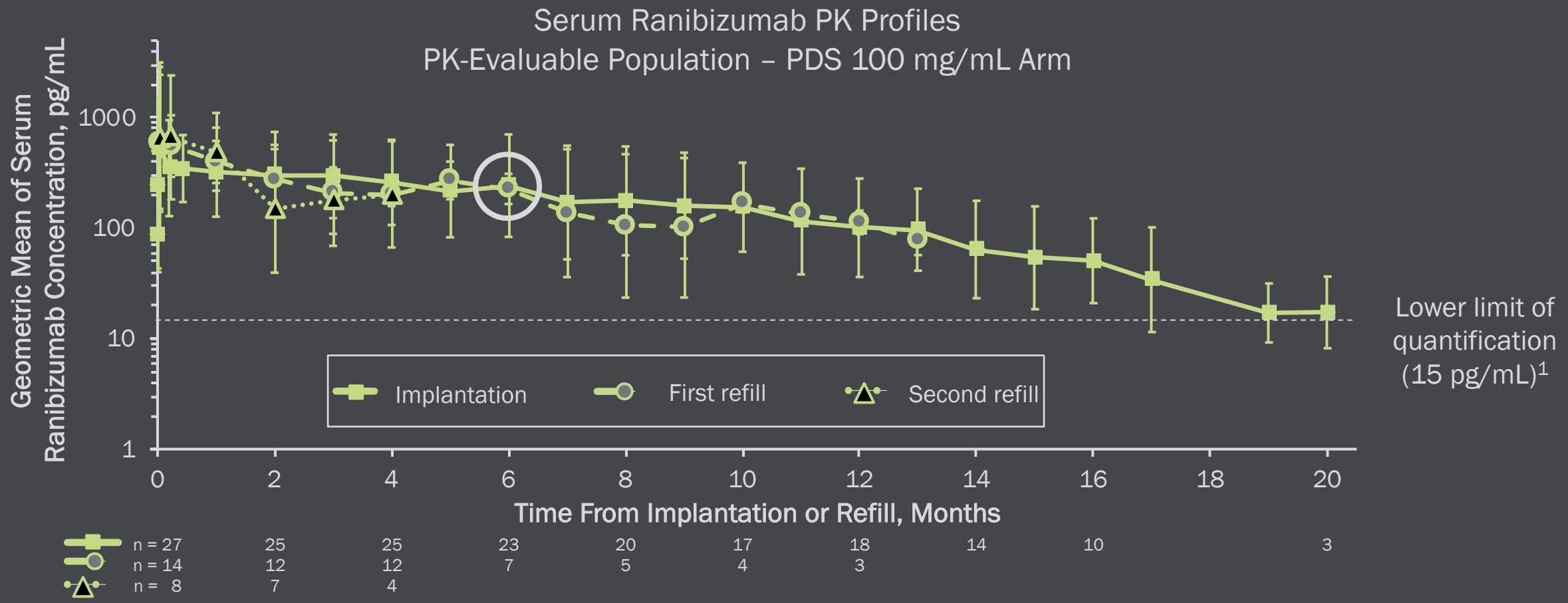
Consistent Serum PK Profile Following Implantation and Multiple Refills



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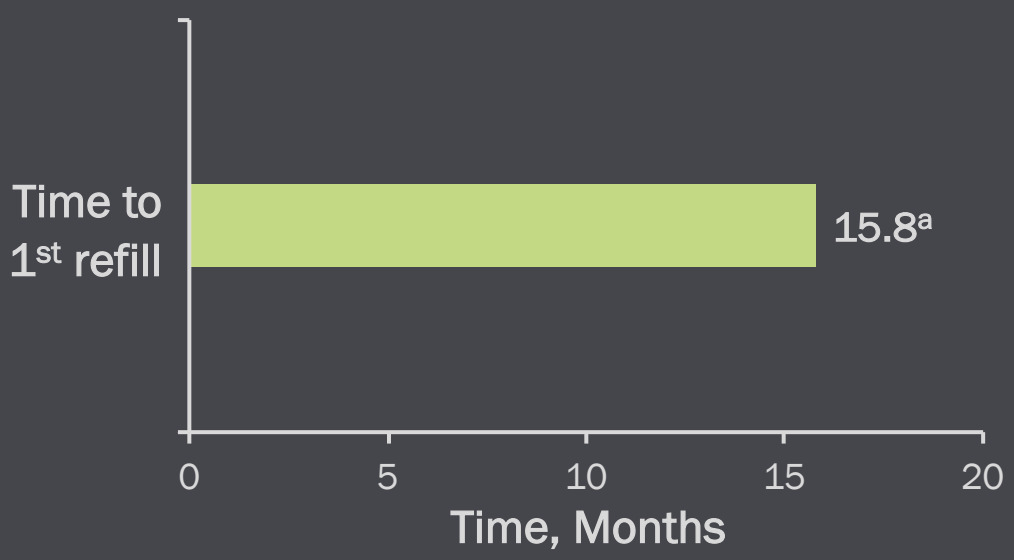
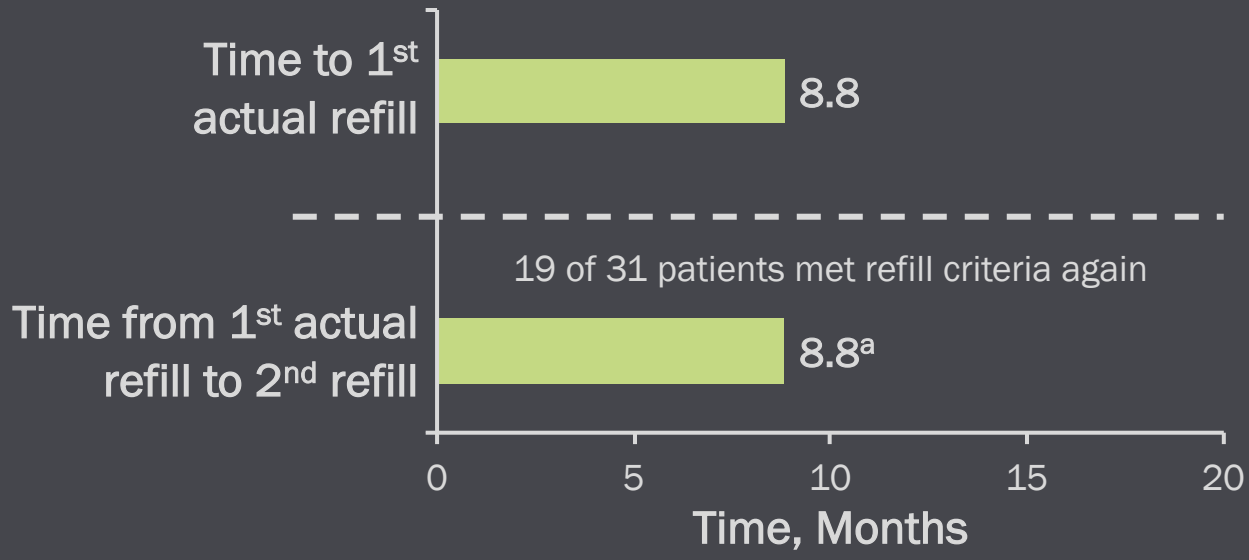
Consistent Time to First and Second Refills in PDS 100 mg/mL Patients Who Received a Refill

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.
KM, Kaplan-Meier; PDS, Port Delivery System with ranibizumab.

The PK Profile of the PDS Correlates With Observed Durability and Efficacy Outcomes in Ladder

- **Comparable:** Serum concentrations with PDS 100 mg/mL are within the range of concentrations of monthly intravitreal ranibizumab injections through at least 12 months following implantation and are measurable in serum past 16 months
- **Consistent:** Serum PK profiles are consistent following implantation and multiple refills in line with the time to first and second refills

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

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

Median time to first refill of 15.8 was observed in the PDS 100 mg/mL arm.
nAMD, neovascular age-related macular degeneration; PDS, Port Delivery System with ranibizumab; PK, pharmacokinetic.

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