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

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\textsuperscript{2} Genentech, Inc., South San Francisco, CA
Disclosures

Financial disclosures


Study disclosures

- 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 Karlina J. Kauffman, PhD, of Envision Pharma Group
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.
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

<table>
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<tr>
<th>PDS with ranibizumab 10 mg/mL</th>
<th>PDS with ranibizumab 40 mg/mL</th>
<th>PDS with ranibizumab 100 mg/mL</th>
<th>Monthly intravitreal ranibizumab 0.5 mg</th>
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<td>( n = 58 )</td>
<td>( n = 62 )</td>
<td>( n = 59 )</td>
<td>( n = 41 )</td>
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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)

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\(^a\) ≥ 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

- **PDS Arms** (10, 40, and 100 mg/mL)
- **ITV Arm**

**Time, Months**
0 1 2 3 4 5 6 7 8 9a 22b

**PRN Refill**

- **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\text{\text{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.

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2. C\text{\text{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.

Half-Lives

- Vitreous: ≈ 100+ days
- Serum: ≈ 7 days
- Serum: ≈ 2 hours
PDS Implant Continues to Release Ranibizumab Through At Least Month 16 in the PDS 100 mg/mL Arm

Serum Ranibizumab PK Profiles (Without Refill)

PK-Evaluable Population

Geometric Mean of Serum Ranibizumab Concentration, pg/mL

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.

Lower limit of quantification (15 pg/mL)

Vertical bars represent the geometric mean ± geometric SD.

2. PDS, Port Delivery System with ranibizumab; PK, pharmacokinetic.
Concentrations With PDS 100 mg/mL Within the Range Seen With Monthly Intravitreal Ranibizumab Injections

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.


Median Serum Ranibizumab Concentration, pg/mL
Serum PK Profiles Based on Time on Study
Full Study Population (Independent of Refill Time)

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

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Full Study Population (Independent of Refill Time)

Mean Time on Study = 22.1 Months for All PDS Patients (Range, 10.8–37.6 Months)
Concentrations With PDS 100 mg/mL Within the Range Seen With Monthly Intravitreal Ranibizumab 0.5 mg

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.


C<sub>trough</sub>, serum trough concentration; PDS, Port Delivery System with ranibizumab; PK, pharmacokinetic.

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C<sub>trough</sub>, serum trough concentration; PDS, Port Delivery System with ranibizumab; PK, pharmacokinetic.
PDS Continuously Delivers Ranibizumab for Extended Durations Consistently Across PDS 100 mg/mL Patients

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.

PDS, Port Delivery System with ranibizumab; PK, pharmacokinetic.
Consistent Serum PK Profile Following Implantation and Multiple Refills

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

Time to 1st refill

Time from 1st actual refill to 2nd refill

Time to 1st actual refill

19 of 31 patients met refill criteria again

\[ \text{Time to 1st actual refill} = 8.8 \]

\[ \text{Time from 1st actual refill to 2nd refill} = 8.8^a \]

* 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.
Thank You to All Participating Principal Investigators and Research Teams and Patients at Study Sites

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