Long-Acting Ocular Drug Delivery: Port Delivery System for Ranibizumab

Virtual On Demand
Shrirang Ranade, PhD
Session Description and Objectives

The Port Delivery System with ranibizumab (PDS) is a combination product, comprising an ocular implant, a customized formulation of ranibizumab, and 4 ancillary devices (insertion tool assembly, initial fill needle, refill needle, and explant tool). The surgically placed implant enables continuous delivery over several months and showed equivalent and noninferior performance to monthly intravitreal ranibizumab injections in the treatment of nAMD. The implant is permanent and can be refilled in situ.

Upon completion, the participant will be able to:

- Understand development of novel drug delivery systems for successful delivery to the back of the eye
- Learn about successful phase 3 clinical trials using a long-term delivery device
- Understand the basic pharmacokinetic considerations for ocular delivery
- Understand the technology and development of the Port Delivery System
Biography and Contact Information

Shrirang (Shri) Ranade, PhD, is a Director in Projects & Portfolio Management in Pharma Technical Development at Genentech/Roche and serves as the Sr. Technical Development Team Leader for the Port Delivery System with ranibizumab

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Disclosures

Financial Disclosures
• SR: Employee: Genentech, Inc.

Study Disclosures
• PDS is an investigational medicine that is being studied for the treatment of neovascular age-related macular degeneration, diabetic retinopathy, and diabetic macular edema. Its efficacy and safety profile have not been established and it has not been approved by the health authorities
• 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 Dionne Turnbull, PhD, of Envision Pharma Group
Contents

1. Background:
   a. The Unmet Need for Long-Acting Retinal Drug Delivery
   b. Ocular Drug Delivery Routes

2. The Port Delivery System With Ranibizumab
   a. Design Features
   b. Mechanism of Continuous Delivery
   c. The PDS in Clinical Studies

3. In Vitro Testing of Ranibizumab Release From the PDS Implant
   a. Tunable Drug Release Based on Starting Concentration
   b. Consistency of Release After Refill-Exchange
   c. Efficiency of the Refill-Exchange Procedure

4. PDS Clinical Trial Data: Pharmacokinetics, and Vision Outcomes

5. Conclusions
Visual Gains Seen in Clinical Trials Are Not Replicated in Real-world Clinical Practice

### Clinical Trials1-9 vs Real-world Studies10-13

#### 1-year outcomes with ranibizumab 0.5 mg

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean BCVA Change From Baseline, ETDRS Letters</th>
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<tbody>
<tr>
<td>ANCHOR Monthly</td>
<td>11.3</td>
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<tr>
<td>MARINA Monthly</td>
<td>7.2</td>
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<tr>
<td>HARBOR Monthly</td>
<td>10.1</td>
</tr>
<tr>
<td>VIEW1/2 Monthly</td>
<td>8.7</td>
</tr>
<tr>
<td>CATT Monthly</td>
<td>8.5</td>
</tr>
<tr>
<td>HARBOR PRN</td>
<td>8.2</td>
</tr>
<tr>
<td>CATT PRN</td>
<td>6.8</td>
</tr>
<tr>
<td>AURA Real world</td>
<td>2.4</td>
</tr>
<tr>
<td>LUMIERE Real world</td>
<td>3.2</td>
</tr>
<tr>
<td>WAVE Real world</td>
<td>-0.8</td>
</tr>
</tbody>
</table>

Number of ranibizumab injections:
- ANCHOR Monthly: 12
- MARINA Monthly: 12
- HARBOR Monthly: 11.3
- VIEW1/2 Monthly: 11.8
- CATT Monthly: 11.7
- HARBOR PRN: 7.7
- CATT PRN: 6.9
- AURA Real world: 5.0
- LUMIERE Real world: 5.1
- WAVE Real world: 4.3

The PDS has the potential to reduce treatment burden and address suboptimal visual outcomes in the real world.


BCVA, best-corrected visual acuity; CATT, Comparison of Age-related Macular Degeneration Treatments Trials; ETDRS, Early Treatment Diabetic Retinopathy Study; PDS, Port Delivery System with ranibizumab.
nAMD Anti-VEGF Treatment: Treatment Patterns and Efficacy in Clinical Practice Differ From RCTs


- Real-world VA 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

**Mean Injections Over 2 Years¹**

<table>
<thead>
<tr>
<th>Country</th>
<th>Mean Injections</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Kingdom (n = 410)</td>
<td>9.0</td>
</tr>
<tr>
<td>Netherlands (n = 350)</td>
<td>8.7</td>
</tr>
<tr>
<td>Total (n = 2227)</td>
<td>7.2</td>
</tr>
<tr>
<td>France (n = 398)</td>
<td>6.3</td>
</tr>
<tr>
<td>Germany (n = 398)</td>
<td>5.6</td>
</tr>
<tr>
<td>Italy (n = 365)</td>
<td>5.2</td>
</tr>
</tbody>
</table>


ETDRS, Early Treatment Diabetic Retinopathy Study; LOCF, last observation carried forward; nAMD, neovascular age-related macular degeneration; RCT, randomized controlled trial; VA, visual acuity; VEGF, vascular endothelial growth factor.

Undertreatment in clinical practice results in worse visual outcomes for nAMD compared with clinical trials.
Routes of Administration for Ocular Drug Delivery
Multiple Options for LAD of Biologics

**Formulation-Based Approaches**
- Polymer-based microparticles
- Polymer-based nanoparticles
- **✓ Polymer-based implants**
- In situ gelling systems
- Complexation
- Lipid-based systems
- Silicon-based systems

**Molecular Conjugation Approaches**
- **✓ Reservoir (passive diffusion)**
- Pumps (active diffusion)
- Reversible conjugation to:
  - Polymer carrier (hydrogel or microspheres)
- Permanent conjugation/fusion to:
  - Polymers
  - Proteins

**Implanted Devices**
- Bioreactors (in situ production)
- **✓ Reservoir (passive diffusion)**
- Pumps (active diffusion)

LAD, long-acting delivery.
The Port Delivery System With Ranibizumab (PDS)

- Innovative, investigational drug delivery system that enables continuous delivery of ranibizumab into the vitreous
- Includes a customized formulation of ranibizumab, an ocular implant, and 4 ancillary devices:
  1. Insertion tool assembly
  2. Initial fill needle
  3. Refill needle
  4. Explant tool
Design Features of the PDS Implant

The PDS implant is intentionally designed to be:

- Permanent, biocompatible, and durable
- Transparent to facilitate visualization of ranibizumab solution within the reservoir (implant contains 20 µL)
- Refillable via the self-sealing septum
- Noninterfering with the patient’s field of vision
- Covered by eyelid, not visible in primary gaze
Why Ranibizumab Is the Right Drug for the PDS

Ranibizumab, bevacizumab, and aflibercept were assessed for formation of aggregates and antigen-binding capacity over a 25-week period.

- Ranibizumab shows minimal aggregation over 6 months.
- Ranibizumab exhibits the smallest loss in antigen-binding capacity over 6 months of incubation.

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PDS, Port Delivery System with ranibizumab.
Why the PDS Is the Right Technology for Ranibizumab Delivery

- Drug release kinetics are dependent on a combination of drug concentration and properties of the release control element (porosity, length, and tortuosity)
- Consistent, predictable, tunable, and sustained release of ranibizumab is obtained over several months
PDS Mechanism of Continuous Delivery: Passive Diffusion

- Continuous delivery mediated by passive diffusion along a concentration gradient
- Rate of diffusion is concentration dependent and decreases over time

Diagram for illustrative purposes only.
PDS, Port Delivery System with 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

Half-Lives

- ≈ ≥ 100 days
- ≈ 7 days
- ≈ 2 hours

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.
Ladder Phase 2 and Archway Phase 3 Trials of the PDS

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

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

Randomized 3:3:3:2

PRN re-treatment (refill)

Primary endpoint: Time to first PDS refill
Assessed when last patient completed month 9 visit

Patients with nAMD responsive to any anti-VEGF treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDS with ranibizumab 100 mg/mL with fixed refill-exchanges Q24W</td>
<td>n = 248</td>
</tr>
<tr>
<td>Intravitreal ranibizumab 0.5 mg Q4W</td>
<td>n = 167</td>
</tr>
</tbody>
</table>

Randomized 3:2

Weeks 36 and 40: primary endpoint
Week 96: final visit

Primary endpoint: Change in BCVA score from baseline
Averaged over weeks 36 and 40

Several large-scale clinical trials are ongoing for the PDS 100 mg/mL: Velodrome and Portal (nAMD), Pavilion (DR without DME), and Pagoda (DME)

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 Ladder 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. Ladder, NCT02510794.
c Modified intent-to-treat population for safety analyses. 418 total patients were enrolled, with 251 and 167 patients randomized to the PDS 100 mg/mL Q24W and intravitreal ranibizumab 0.5 mg Q4W arms, respectively; 3 patients in the PDS arm did not receive study treatment and were excluded from the efficacy- and safety-evaluable population. Archway, NCT03677934. BCVA, best-corrected visual acuity; DME, diabetic macular edema; DR, diabetic retinopathy; nAMD, neovascular age-related macular degeneration; PDS, Port Delivery System with ranibizumab; PRN, as-needed; Q4W, every 4 weeks; Q24W, every 24 weeks; VEGF, vascular endothelial growth factor.
In Vitro Testing Was Used to Verify Release Rates With Different Ranibizumab Concentrations

- Implants filled per the clinical Instructions for Use were regularly transferred to new buffer-containing vials
- A Bradford assay was used to measure released ranibizumab concentrations in each vial
- The activity of ranibizumab released from implants was determined by a Biacore assay
- Release rate data were fit using an exponential model to mimic the expected release kinetics of diffusion and were compared with predicted release rate kinetics

Target ranibizumab release rates were selected by leveraging clinical and PK data from trials with intravitreal ranibizumab injections

PK, pharmacokinetic.
Drug Release From the PDS Is Dependent on the Starting Concentration of Ranibizumab

Theoretical drug-release curves, calculated based on first-order drug-release kinetics.

PDS, Port Delivery System with ranibizumab.

*Theoretical drug release curves, calculated based on first-order drug-release kinetics.
PDS, Port Delivery System with ranibizumab.
Active Release Rate of Ranibizumab From the PDS is Consistent Across Treatment Cycles

- Release rate decreases over time because it is concentration dependent.
- Release rate is consistent across treatment cycles.
- Release rates with ranibizumab 100 mg/mL ensure that the ranibizumab concentration in the vitreous is maintained within therapeutic levels across 24-week treatment cycles.

Error bars show SD.

PDS, Port Delivery System with ranibizumab.
The PDS Releases Ranibizumab 100 mg/mL Consistently In Vitro Across 24-Week Treatment Cycles

Cumulative release: the total amount of ranibizumab released up to a time point, expressed as the percentage of the drug originally loaded into the implant.

Levels of ranibizumab 100 mg/mL in the implant were below the lower level of quantification after 450 days.

PDS, Port Delivery System with ranibizumab.

~70% of ranibizumab 100 mg/mL was released from the PDS over 6 months following initial fill.

Ranibizumab 100 mg/mL release after refill-exchange is consistent with the initial fill.
Ranibizumab Was Continuously Released and Detectable Across 24-Week Treatment Cycles and Beyond

- Cumulative ranibizumab release was ~75% by month 6
- Cumulative ranibizumab release was ~87% by month 9

PDS, Port Delivery System with ranibizumab.
Each Refill-Exchange Replaces ~99% of Implant Content With Fresh Drug

PDS, Port Delivery System with ranibizumab.
Ladder Phase 2 Trial: Serum Ranibizumab PK Profiles Were Consistent With In Vitro Release Data

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 received 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 \( \div \) geometric SD. Model projection generated based on updated population PK analysis (including data from study FVF4579g).


Please see poster by Maass et al
Ladder Phase 2 Trial: Time to First Meeting Refill Criteria was 15.8 Months in the PDS 100 mg/mL Arm

BCVA Results Were Comparable With Monthly Ranibizumab Injections Over a Mean 22 Months on Study

Median Time to First Refill

<table>
<thead>
<tr>
<th>Refill Criteria, Months</th>
<th>PDS ranibizumab 10 mg/mL</th>
<th>PDS ranibizumab 40 mg/mL</th>
<th>PDS ranibizumab 100 mg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8.7</td>
<td>13.0</td>
<td>15.8</td>
</tr>
</tbody>
</table>

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

Observed Mean BCVA Change From Baseline

Previously Anti-VEGF Treated^{b}

<table>
<thead>
<tr>
<th>Time, Months</th>
<th>PDS ranibizumab 10 mg/mL</th>
<th>PDS ranibizumab 40 mg/mL</th>
<th>PDS ranibizumab 100 mg/mL</th>
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</thead>
<tbody>
<tr>
<td>Post-op day 1</td>
<td>n = 62</td>
<td>n = 60</td>
<td>n = 59</td>
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<tr>
<td></td>
<td>58</td>
<td>61</td>
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<table>
<thead>
<tr>
<th>Time, Months</th>
<th>Monthly intravitreal ranibizumab 0.5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-op day 1</td>
<td>n = 41</td>
</tr>
<tr>
<td></td>
<td>40</td>
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<tr>
<td>3</td>
<td>41</td>
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<td>18</td>
<td>29</td>
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<td>21</td>
<td>20</td>
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^{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. ^{b} 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; ETDRS, Early Treatment Diabetic Retinopathy Study; PDS, Port Delivery System with ranibizumab; post-op, post operation; VEGF, vascular endothelial growth factor.
Archway Phase 3 Trial: Mean Ranibizumab Concentrations Were Steady and Continuous Over the Refill-Exchange Interval With PDS 100 mg/mL Q24W

Serum Ranibizumab PK Profiles (PK-Evaluable Population)

Vertical bars represent the geometric mean */ geometric SD. PK-evaluable population included patients who did not receive ranibizumab as supplemental treatment in the study eye after implant insertion or in the fellow eye, or prior intravitreal bevacizumab treatment.


PDS, Port Delivery System with ranibizumab; PK, pharmacokinetic; Q4W, every 4 weeks; Q24W, every 24 weeks.
Archway Phase 3 Trial: Continuous Ranibizumab Release Resulted in Consistent Clinical Outcomes Across Treatment Cycles
PDS Q24W Maintained Vision and Anatomic Outcomes Comparable With Monthly Ranibizumab Through Week 48

Mean of 5.0 Previous Anti-VEGF Injections

- Primary endpoint: PDS Q24W was noninferior and equivalent for BCVA change at the average of weeks 36/40
- BCVA change at the average of weeks 44/48 remained noninferior through 2 refill-exchange intervals
- CPT outcomes were comparable across arms

CPT defined as retinal thickness in the center of the fovea measured between the internal limiting membrane and the inner third of the retinal pigment epithelium layer. Adjusted means were estimated using a mixed-effect model for repeated measures with adjustment for change from baseline in CPT score as the response and included terms for treatment group, visit, treatment-by-visit interaction, and baseline BCVA (< 74 ETDRS letters vs ≥ 74 ETDRS letters).

BCVA, best-corrected visual acuity; CPT, center point thickness; 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.
Conclusions

The PDS is an innovative, investigational ocular drug delivery system that continuously and reproducibly delivers ranibizumab into the vitreous over a period of ≥ 6 months via diffusion-mediated release kinetics.

- Ranibizumab release from the PDS implant was demonstrated to be highly predictable and tunable, based on a simple diffusion model.
- ~70% of the original ranibizumab 100 mg/mL load is released during a 6-month period.
- Release rate changes gradually, from ~17 µg/day to ~4 µg/day, due to continuously decreasing ranibizumab concentration inside the implant.
- These release rates ensure that the ranibizumab concentration in the vitreous is maintained within therapeutic levels.
- The residual ranibizumab solution in the implant can be reproducibly exchanged (~99%) with fresh ranibizumab, with refilled implant performance comparable with that of the implant after initial fill.
- These in vitro results support the median time to first refill of 15.8 months in the PDS 100 mg/mL arm of the phase 2 Ladder trial, and support the fixed 24-week refill-exchange intervals in the Archway trial.
- Archway phase 3 trial results support the efficacy of the PDS, with PDS Q24W shown to deliver vision and anatomic outcomes comparable with monthly ranibizumab averaged over weeks 44/48.

PDS, Port Delivery System with ranibizumab; Q4W, every 4 weeks; Q24W, every 24 weeks.
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