Long-Term Efficacy and Safety of the Port Delivery System With Ranibizumab (PDS) in Patients With Neovascular Age-Related Macular Degeneration (nAMD): Results From the Portal 5-Year Subgroup Analysis

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Disclosures

Financial Disclosures

- GC: Consultant: Allergan, Bayer, Boehringer Ingelheim, Iveric Bio, Novartis, Roche, Topcon, Zeiss
- JN: Research Support: Alexion, Eyepoint Pharmaceuticals, Gemini Therapeutics, Genentech, Gyroscope Therapeutics, Iveric Bio, Kodiak Scientific, Novartis, Novo Nordisk, Regeneron, Regenxbio, Roche; Consultant/Advisory Board: Iveric Bio, Regeneron; Speakers Bureau: Apellis, Genentech
- JH: Consultant: Genentech, Inc.; Speaker honoraria: Genentech, Inc.
- MCC, NS, SG: Employee, Stockholder: Genentech, Inc.

Study and Product Disclosures

- The Port Delivery System with ranibizumab (PDS) has been approved by the US Food and Drug Administration for the treatment of nAMD in adults who have previously responded to ≥ 2 anti-VEGF injections. Please note that the PDS has not been approved for use outside of the United States.
  - Roche/Genentech has voluntarily recalled the PDS (Susvimo) Ocular Implant and Insertion Tool Assembly, including the ranibizumab drug vial and initial fill needle (lot numbers 3499188 and 3523071), which are sold together, and paused implantations including in ongoing global clinical trials.
- The US Food and Drug Administration has issued a boxed warning for the PDS because it has been associated with a 3-fold higher rate of endophthalmitis compared with monthly intravitreal injections of ranibizumab.
- 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 Jeannine Delwiche, PhD, and Elizabeth Daniel, PhD, of Envision Pharma Group.


nAMD, neovascular age-related macular degeneration; PDS, Port Delivery System with ranibizumab; VEGF, vascular endothelial growth factor.
Continuous Delivery Via the Port Delivery System With Ranibizumab

Innovative Drug Delivery System

- Refillable ocular implant for **continuous delivery** of a customised formulation of ranibizumab 100 mg/mL
- In-clinic refill-exchange procedures once or twice a year

PDS Path Forward

- Clinical trials, including Velodrome\(^1\) and Diagrid\(^2\), are aiming to resume globally as soon as possible (subject to local health authority approval) following improvements to manufacturing processes

Long-Term Efficacy of the PDS

- Long-term efficacy and safety of Ladder-to-Portal patients with nAMD treated with the PDS for > 5 years

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Eligible patients\(b\) from Ladder:

**PDS-implanted patients**

- PDS 100 mg/mL PRN
- PDS 40 mg/mL PRN
- PDS 10 mg/mL PRN

**Monthly ranibizumab 0.5 mg\(c\)**

- Intravitreal 0.5 mg

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**Safety Population with ≥5 Years Follow-up**  
\(n = 114\)

All Ladder patients\(f\) with PDS ≥5 years treatment and implanted after IFU V10

**Efficacy Population PDS 100 mg/mL ≥5 Years Follow-up**  
\(n = 46\)

All patients treated with PDS 100 mg/mL in Ladder and completed ≥5 years treatment

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**Follow-up over 5 study years\(e\)**
Baseline BCVA of 20/40 Snellen Maintained Over 5 Years (60 months) in Patients Who Received PDS 100 mg/mL Q24W

Mean Change From Baseline in BCVA, Ladder Efficacy Population
All patients received 3 injections prior to baseline

Month 0 Observed BCVA
70.6 Letters (20/40)

Month 60 Observed BCVA
68.8 Letters (20/40)

Prior PDS 100 mg/mL (n = 46)

Follow-up after 42 months ongoing

All Ladder data to month 12
Mixed Ladder/Portal data with variable time to roll over into Portal
All Portal data from month 38

n = 46 45 46 45 46 46 45 46 46 46 46 46 46 46 46 46 46 46 46 46 46 46 46 46 46 46 46 42 38 28 20 17

Visit, Months

Ladder, NCT02510794; Portal, NCT0368325. Ladder efficacy population. Observed data. Baseline is defined as the last assessment on or before the first study treatment in Ladder. Target visit dates are spaced 30 days apart in Ladder assessments and 56 days apart for Portal assessments. Last observation carried forward was used for intermittent missing values during Portal to correct for the difference in visit schedules. The bars represent multiplicity-adjusted 95% CI with Bonferroni correction. BCVA, best corrected-visual acuity; CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study; PDS, Port Delivery System with ranibizumab; Q24W, every 24 weeks.
CPT Remained Stable Over 5 years (60 Months) in Patients Who Received PDS 100 mg/mL Q24W

Mean Change From Baseline in CPT, Ladder Efficacy Population

All patients received 3 injections prior to baseline

Month 0 Observed CPT
Mean (SD), μM: 174.2 (60.9)

Month 60 Observed CPT
Mean (SD), μM: 162.4 (58.4)

Visit, Months

Mean Change From Baseline in CPT, µm

Prior PDS 100 mg/mL PRN (n = 46)

All Ladder data to month 12
Mixed Ladder/Portal data with variable
time to roll over into Portal
All Portal data from month 38
Follow-up after 42 months ongoing

n = 46 42 44 45 44 46 45 45 44 43 46 46 46 46 46 46 46 46 46 46 46 46 46 46 45 41 38 28 20 17

Ladder, NCT02510794; Portal, NCT03683251. Ladder efficacy population. Observed data. Baseline is defined as the last assessment on or before the first study treatment in Ladder. Target visit dates are spaced 30 days apart in Ladder assessments and 56 days apart for Portal assessments. Last observation carried forward was used for intermittent missing values during Portal to correct for the difference in visit schedules. The bars represent multiply-adjusted 95% CIs by Bonferroni correction. CPT assessed by the central reading center with boundaries internal limiting membrane to inner third of the retinal pigment epithelium. CI, confidence interval; CPT, center point thickness; PDS, Port Delivery System with ranibizumab; Q24W, every 24 weeks.
~95% of Patients Did Not Receive Supplemental Treatment Through Each Refill-Exchange Interval During Portal®

These data are from the fixed dosing phase in Portal that followed PRN refills in Ladder

Proportion of Patients Not Receiving Supplemental Treatment Through Week 144 (6 Refill-Exchange Intervals); Ladder Efficacy Population

Ladder, NCT02510794; Portal, NCT03683251. Observed data through the July 2022 clinical cutoff date; data collection ongoing. * Eligible for supplemental intravitreal ranibizumab treatment with open-label intravitreal ranibizumab if any of the following 3 criteria were met: (1) decrease of ≥ 15 letters from the best-corrected visual acuity (BCVA) in the study; (2) increase of ≥ 150 µm in central subfield thickness (CST) on spectral-domain optical coherence tomography (SD-OCT) from the lowest CST measurement in the study; or (3) increase of ≥ 100 µm in CST on SD-OCT from the lowest CST measurement in the study associated with a decrease of ≥ 10 letters from the best-recorded BCVA during the study. Patients assessed from day 1 to week 24. ** Patients assessed from weeks 25 to 48. *** Patients assessed from weeks 49 to 72. **** Patients assessed from weeks 73 to 96. ***** Patients assessed from weeks 97 to 120. ****** Patients assessed from weeks 121 to 144. Excludes patients who missed assessments at weeks 24, 48, 72, 96, or 144 or who discontinued treatment early. BCVA, best-corrected visual acuity; CST, central subfield thickness; PDS, Port Delivery System with ranibizumab; PRN, pro re nata (as needed); Q24W, every 24 weeks; SD-OCT, spectral-domain optical coherence tomography.

Prior PDS 100 mg/mL  All Ladder-implanted PDS patients

Number of patients assessed for supplemental treatment during interval:

<table>
<thead>
<tr>
<th>Refill-Exchange Interval</th>
<th>46</th>
<th>126</th>
<th>46</th>
<th>126</th>
<th>41</th>
<th>115</th>
<th>46</th>
<th>123</th>
<th>45</th>
<th>122</th>
<th>46</th>
<th>121</th>
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</thead>
<tbody>
<tr>
<td>Refill-Exchange Interval 1</td>
<td>100</td>
<td>98.4</td>
<td>95.7</td>
<td>97.6</td>
<td>100</td>
<td>97.4</td>
<td>97.8</td>
<td>96.7</td>
<td>97.8</td>
<td>95.9</td>
<td>93.5</td>
<td>95.0</td>
</tr>
<tr>
<td>Refill-Exchange Interval 2</td>
<td>100</td>
<td>98.4</td>
<td>95.7</td>
<td>97.6</td>
<td>100</td>
<td>97.4</td>
<td>97.8</td>
<td>96.7</td>
<td>95.9</td>
<td>95.0</td>
<td>93.5</td>
<td>95.0</td>
</tr>
<tr>
<td>Refill-Exchange Interval 3</td>
<td>100</td>
<td>98.4</td>
<td>95.7</td>
<td>97.6</td>
<td>100</td>
<td>97.4</td>
<td>97.8</td>
<td>96.7</td>
<td>95.9</td>
<td>95.0</td>
<td>93.5</td>
<td>95.0</td>
</tr>
<tr>
<td>Refill-Exchange Interval 4</td>
<td>100</td>
<td>98.4</td>
<td>95.7</td>
<td>97.6</td>
<td>100</td>
<td>97.4</td>
<td>97.8</td>
<td>96.7</td>
<td>95.9</td>
<td>95.0</td>
<td>93.5</td>
<td>95.0</td>
</tr>
<tr>
<td>Refill-Exchange Interval 5</td>
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<td>98.4</td>
<td>95.7</td>
<td>97.6</td>
<td>100</td>
<td>97.4</td>
<td>97.8</td>
<td>96.7</td>
<td>95.9</td>
<td>95.0</td>
<td>93.5</td>
<td>95.0</td>
</tr>
<tr>
<td>Refill-Exchange Interval 6</td>
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<td>98.4</td>
<td>95.7</td>
<td>97.6</td>
<td>100</td>
<td>97.4</td>
<td>97.8</td>
<td>96.7</td>
<td>95.9</td>
<td>95.0</td>
<td>93.5</td>
<td>95.0</td>
</tr>
</tbody>
</table>
Ocular Adverse Events of Special Interest<sup>a</sup> From Time of Implant Insertion: Ladder-Implanted PDS Patients with ≥ 5 Years<sup>b</sup> Follow-Up

<table>
<thead>
<tr>
<th>MedDRA Preferred Term&lt;sup&gt;c&lt;/sup&gt;</th>
<th>All Ladder-Implanted Patients with PDS ≥5 Years&lt;sup&gt;b&lt;/sup&gt; (July 2022 Data-cut); &lt;i&gt;n = 114&lt;/i&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall number of AESIs</td>
<td>76</td>
</tr>
<tr>
<td>Mean (SD) follow-up time, weeks</td>
<td>276.3 (17.2)</td>
</tr>
<tr>
<td>Total number of patients with ≥ 1 AESI, n (%)</td>
<td>47 (41.2) 1 (0.9)</td>
</tr>
<tr>
<td>Cataract&lt;sup&gt;d&lt;/sup&gt;</td>
<td>31 (27.2) 0</td>
</tr>
<tr>
<td>Conjunctival bleb/conjunctival filtering bleb leak</td>
<td>7 (6.1) 0</td>
</tr>
<tr>
<td>Vitreous hemorrhage</td>
<td>8 (7.0) 0</td>
</tr>
<tr>
<td>Conjunctival erosion</td>
<td>10 (8.8) 0</td>
</tr>
<tr>
<td>Conjunctival retraction</td>
<td>1 (0.9) 0</td>
</tr>
<tr>
<td>Endophthalmitis&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0 0</td>
</tr>
<tr>
<td>Implant dislocation</td>
<td>0 0</td>
</tr>
<tr>
<td>Septum dislodgement</td>
<td>0 0</td>
</tr>
<tr>
<td>Hyphema</td>
<td>3 (2.6) 1 (0.9)</td>
</tr>
<tr>
<td>Rhegmatogenous retinal detachment</td>
<td>1 (0.9) 0</td>
</tr>
</tbody>
</table>

<sup>a</sup> An AE is considered to be sight-threatening if it is a serious adverse event and meets ≥ 1 the following: (1) causes a decrease of ≥ 30 letters in BCVA (compared with the last assessment of VA prior to the most recent treatment) lasting > 1 hour; (2) requires surgical intervention (ie, conventional surgery, vitrectomy, vitreous tap, or biopsy with intravitreal injection of anti-infective medications, or laser or retinal cryopexy with gas) to prevent permanent loss of sight; (3) associated with severe intraocular inflammation (eg, endophthalmitis, 4+ anterior chamber cell/flare or 4+ cells in the vitreous).

<sup>b</sup> Patients were implanted after the Instructions For Use V10 update, which mandated an incision length of 3.5 mm.

<sup>c</sup> Frequency counts by Preferred Term. Multiple occurrences of the same AE in an individual are counted only once for each column. Includes the following terms: cataract, cataract nuclear, cataract cortical, and cataract subcapsular.

<sup>d</sup> The US Food and Drug Administration has issued a boxed warning to the PDS because it has been associated with a 3-fold higher rate of endophthalmitis compared with monthly intravitreal injections of ranibizumab. All adverse events (AEs) adverse event of special interest; BCVA, best-corrected visual acuity; CCOD, clinical cutoff date; MedDRA, Medical Dictionary for Regulatory Activities; PDS, Port Delivery System with ranibizumab; SD, standard deviation; V, version; VA, visual acuity; Susvimo [prescribing information]. South San Francisco, CA; Genentech, Inc.; 2022.
Clinical Studies of PDS are Now Resuming

**Voluntary Recall**
- Roche/Genentech Inc. voluntarily recalled the PDS Ocular Implant and Insertion Tool Assembly after identifying that implants did not meet pre-specified standards.

**Updated Refill Needle and Implant**
- PDS implant and refill needle component-level updates, manufacturing process improvements, and additional quality control processes, to ensure integrity of every implant manufactured.

**Performance testing completed**
- High confidence of long-term septum durability that mitigates the risk of septum dislodgement. Implantations in clinical studies of PDS resuming upon local Health Authority and Ethics Committee approval.
The efficacy and safety profile of PDS 100 mg/mL was maintained over 5 years of follow-up.

With PDS manufacturing improvements finalised, implantations in clinical trials are expected to resume as soon as possible.\(^a\)