Macular Atrophy (MA) in the Phase 2 Ladder Trial

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<tr>
<th>Aaberg Jr., Thomas</th>
<th>Antoszyk, Andrew</th>
<th>Awh, Carl C.</th>
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Disclosures

- **Financial disclosures**
  - GJJ: Consultant) Novartis, EyePoint, Neurotech, Iveric, Clearside.
  - GB, CYL, SG: Employee) 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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Summary-Key Takeaways
Macular Atrophy (MA) in the Phase 2 Ladder Trial

- Continuous ranibizumab delivery via the PDS does not cause more atrophy than monthly injections
- Comparable rates of MA incidence, size, enlargement
Macular Atrophy in Eyes With nAMD Receiving Anti-VEGF Treatment

- Macular atrophy definition
- MA in IVAN, CATT, and HARBOR trials
- What about continuous delivery?
Purpose

- Macular atrophy incidence, size, and enlargement in PDS vs monthly ranibizumab injections
The Port Delivery System With Ranibizumab (PDS)

► Continuous drug delivery system
  - Permanent, refillable intraocular implant
  - Customized ranibizumab formulation
  - Implant surgically placed at the pars plana
  - In office refill-exchange procedure
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
N = 220
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

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

Secondary endpoints
Change from BL in BCVA
Change from BL in CFT
Safety

PDS refill criteria
Increase in CFT
Decrease in BCVA
New macular hemorrhage

Last assessment varied due to variable time on study (mean = 22.1 months for all PDS patients (range, 10.8–37.6 months)
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 type¹

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Randomized 3:3:3:2

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Monthly intravitreal ranibizumab 0.5 mg
n = 41

PRN re-treatment (refill)

Monthly injections

Ladder phase 2 trial
► PDS 100 mg/mL vision and anatomic outcomes comparable with monthly ranibizumab
► PDS was generally well tolerated
► Supported evaluation in Archway phase 3 trial

Macular Atrophy in Ladder Assessed at Screening, Months 4 and 9, and Last Assessment

- DRC assessed MA
- Two readers assessed MA, MA area
  - Third reader arbitrated values that differed >10%
  - Areas differing by ≤10% were averaged
- SDOCT: MA presence according to CAM
- FAF: MA area
- The worst-observation-carried-forward approach was used to impute missing data
RESULTS
% MA Throughout Ladder was Similar Across Treatment Arms

<table>
<thead>
<tr>
<th>Eyes with MA (%)</th>
<th>Baseline</th>
<th>Month 4</th>
<th>Month 9</th>
<th>Last Assessment</th>
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<tbody>
<tr>
<td></td>
<td>14.5</td>
<td>25.0</td>
<td>30.0</td>
<td>38.6</td>
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<tr>
<td></td>
<td>11.5</td>
<td>25.0</td>
<td>28.6</td>
<td>40.0</td>
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<tr>
<td></td>
<td>13.6</td>
<td>24.0</td>
<td>29.1</td>
<td>40.4</td>
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<tr>
<td></td>
<td>7.3</td>
<td>22.2</td>
<td>35.3</td>
<td>45.7</td>
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</table>

n = 8/55 7/61 8/59 3/41 13/52 14/56 12/50 8/36 15/50 16/56 16/55 12/34 22/57 24/60 23/57 16/35

- PDS ranibizumab 10 mg/mL
- PDS ranibizumab 40 mg/mL
- PDS ranibizumab 100 mg/mL
- Monthly intravitreal ranibizumab 0.5 mg
New MA Incidence Similar Across Treatment Arms in Patients Without MA at Baseline

Eyes with MA (%)

Month 4

- PDS ranibizumab 10 mg/mL
- PDS ranibizumab 40 mg/mL

Month 9

- PDS ranibizumab 100 mg/mL

Last Assessment

- Monthly intravitreal ranibizumab 0.5 mg

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<tbody>
<tr>
<td>Month 4</td>
<td>11</td>
<td>14</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Month 9</td>
<td>17</td>
<td>18</td>
<td>17</td>
<td>29</td>
</tr>
<tr>
<td>Last Assessment</td>
<td>29</td>
<td>32</td>
<td>31</td>
<td>41</td>
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PDS 100 mg/mL Mean MA Area Was Similar to Monthly Ranibizumab Injections Throughout Ladder
PDS 100 mg/mL Mean MA Area Similar to Monthly Ranibizumab Injections Throughout Ladder

Monthly intravitreal ranibizumab

Port Delivery System with ranibizumab

1.7 mm²

1.7 mm²
Example of Macular Atrophy Area Change Over Time

Baseline: 0.510 mm²

Month 4: 0.778 mm²

Last Assessment: 1.770 mm²
PDS 100 mg/mL MA Area Change Is Similar to Monthly Ranibizumab Injections

- Vertical bars represent 95% CI

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<th>Month 4</th>
<th>Month 9</th>
<th>Last Assessment</th>
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<tr>
<td>PDS ranibizumab 10 mg/mL</td>
<td>9</td>
<td>11</td>
<td>13</td>
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<tr>
<td>PDS ranibizumab 40 mg/mL</td>
<td>4</td>
<td>8</td>
<td>13</td>
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<tr>
<td>Monthly intravitreal ranibizumab</td>
<td>10</td>
<td>13</td>
<td>16</td>
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Mean MA Change From Baseline (mm²)

- n = 9, 8, 11, 4, 10, 7, 13, 13, 16, 9
Conclusions

- Continuous ranibizumab delivery via the PDS does not cause more atrophy than monthly injections
- Comparable rates of MA incidence, size, enlargement