APL-2 in Geographic Atrophy
12-Month Results

Jeffrey S. Heier, MD
Co-President & Medical Director
Ophthalmic Consultants of Boston
Central inhibition of complement

- **Lectin Pathway**
  - APL-2
  - C3
  - Inflammation

- **Classical Pathway**
  - C3
  - C3b
  - Inflammation
  - C3a

- **Alternative Pathway**
  - C5
  - C5a
  - C5b
  - MAC
  - Cell death, secretion, lysis, or proliferation

- **Antigen uptake by APCs**
  - LFG316 (C5, Novartis)

- **Cell removal**
  - Eculizumab (C5, Alexion)

- **Lampalizumab** (Factor D, Roche)
  - CLG561 (Properdin, Novartis)

**Pathways**:
- Lectin Pathway
- Classical Pathway
- Alternative Pathway
All pathways of complement converge on C3
APL-2 targets C3 centrally in the complement cascade.
Endpoints

Primary Efficacy

• Mean change in square root GA area from baseline to month 12\textsuperscript{1,2}

Primary Safety

• Incidence and severity of ocular and systemic AEs

Key Secondary Endpoints

• Change in best corrected visual acuity
• Incidence of new onset exudative AMD

1. Based on fundus autofluorescence photographs (FAF)
Phase 2 GA – FILLY design

Safety, Tolerability and Evidence of Activity N=240*

Randomized 2:1:2:1

- APL-2 15 mg Monthly (AM) N=80
  - Sham Monthly (SM) N=40
  - APL-2 15 mg Every Other Month (AEOM) N=80
  - Sham Every Other Month (SEOM) N=40

AM = APL-2 monthly; AEOM = APL-2 every other month

Randomization

Treatment Period

Follow up

*Note: 246 total patients enrolled in the Phase 2 Filly Study. 240 patients were planned for enrollment
Primary Efficacy Endpoint = Primary Registration Endpoint

- The primary endpoint is the change in square root of geographic atrophy (GA) lesion size from baseline at month 12

Primary Safety Endpoint

- Number and severity of local and systemic treatment emergent adverse events (TEAE)
FILLY phase II trial

- Preventing complement activation by blocking C3
- Statistically significant data in largest Phase II in GA (n=246)
- Results correlated to treatment frequency
- Increased effect size over time
- No specific genotype driving results
- Further confidence in results from intra-patient control
- Notable response in patients that converted to wet AMD
- Phase III design finalized
FILLY - primary endpoint

**Primary efficacy endpoint is the primary registration endpoint**

The primary endpoint is the change in geographic atrophy (GA) lesion size from baseline at month 12.

**Primary safety endpoint**

Number and severity of local and systemic treatment emergent adverse events (TEAE).

Images taken at:
- 0 months
- 2 months
- 6 months
- 12 months
- 18 months

No injections in the treatment period.
**Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>APL-2 Monthly N=86</th>
<th>APL-2 Every Other Month N=79</th>
<th>Sham Pooled N=81</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral GA, n (%)</td>
<td>71 (85.5%)</td>
<td>64 (82.1%)</td>
<td>72 (90.0%)</td>
</tr>
<tr>
<td>History of CNV in Fellow Eye, n (%)</td>
<td>36 (41.9%)</td>
<td>28 (35.4%)</td>
<td>29 (35.8%)</td>
</tr>
<tr>
<td>GA lesion size, mean, mm² (SD)</td>
<td>8.0 (3.8)</td>
<td>8.9 (4.5)</td>
<td>8.2 (4.1)</td>
</tr>
<tr>
<td>BCVA score, mean letters (SD)</td>
<td>59.8 (15.7)</td>
<td>58.4 (16.0)</td>
<td>59.8 (17.2)</td>
</tr>
<tr>
<td>BCVA score (Snellen equivalent)</td>
<td>20/63</td>
<td>20/80</td>
<td>20/63</td>
</tr>
<tr>
<td>LL-BCVA score, mean letters (SD)</td>
<td>36.3 (16.6)</td>
<td>31.4 (17.1)</td>
<td>33.6 (17.8)</td>
</tr>
</tbody>
</table>

- Groups were well balanced as to age, gender and race
Primary Endpoint: GA Lesion Growth

Modified Intent to Treat population (mITT), Observed, Mixed-Effect Model
A mixed effect model with main effects of treatment, visit and GA lesion at baseline, and interactions of treatment × visit, visit × baseline.
mITT = All subjects receiving at least one injection and having at least one FAF image after day 1

LS Mean (±SE) Change from Baseline in Square Root GA Lesion (mm)

Sham Pooled (n=80)

Month

0 2 6 12

0 0.1 0.2 0.3 0.4

0.35
Primary Endpoint: GA Lesion Growth

![Graph showing the LS Mean (±SE) Change from Baseline in Square Root GA Lesion (mm) over months for APL-2 Monthly (n=84) and Sham Pooled (n=80).]

**APL-2 Monthly (n=84)**

- Month 2: 0.25
- Month 6: 0.35

**Sham Pooled (n=80)**

- Month 2: 0.28
- Month 6: 0.32

**Modified Intent to Treat population (mITT), Observed, Mixed-Effect Model**

A mixed effect model with main effects of treatment, visit and GA lesion at baseline, and interactions of treatment × visit, visit × baseline. mITT = All subjects receiving at least one injection and having at least one FAF image after day 1.

**p=0.008 vs Sham**

28.6%
Primary Endpoint: GA Lesion Growth

Modified Intent to Treat population (mITT), Observed, Mixed-Effect Model
A mixed effect model with main effects of treatment, visit and GA lesion at baseline, and interactions of treatment × visit, visit × baseline.
mITT = All subjects receiving at least one injection and having at least one FAF image after day 1
Post hoc analysis: reduction in GA lesion growth was accelerated from month 6 to 12

Data from subjects with a measurable GA lesion size at both Months 6 & 12. Data as of August 24, 2017
Post hoc analysis: in bilateral GA, monthly APL-2 reduced GA growth compared to contralateral eye.

Mean (±SE) Change from Baseline in Square-root GA Lesion (mm)

- AM-Study vs. Sham-Study: 0.020
- AM-Study vs AM-Fellow: 0.083
- AEOM-Study vs Sham-Study: 0.079
- All other pairs (except AM-S or AEOM-S vs Sham-F): > 0.1

mITT-Bilateral GA, Observed, ANOVA at Month 12. Data as of August 24, 2017
GA growth comparison: fellow eye vs study eye

<table>
<thead>
<tr>
<th>Sham group</th>
<th>Active group 1</th>
<th>Active group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham injections</td>
<td>APL-2 injections every other month</td>
<td>APL-2 injections every month</td>
</tr>
</tbody>
</table>

Lesion growth (mm)

- **Sham group** (N=72)
- **Active group 1** (N=63) 10% Difference p > 0.1
- **Active group 2** (N=69) 23% Difference p = 0.083

Study Fellow

- 2 months
- 6 months
- 12 months
Higher incidence of wet AMD conversion in APL-2 patients with wet AMD in the fellow eye

Incidence of wet AMD in study eye for GA Phase 2 trial subjects

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percent</th>
<th>Eligible Market (%</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>APL-2 Monthly (no exclusions)</td>
<td>18%</td>
<td>100%</td>
<td>15</td>
</tr>
<tr>
<td>APL-2 Monthly (excluding fellow-eye wet AMD**)</td>
<td>10%</td>
<td>73%</td>
<td>5</td>
</tr>
<tr>
<td>APL-2 EOM (no exclusions)</td>
<td>8%</td>
<td>100%</td>
<td>6</td>
</tr>
<tr>
<td>APL-2 EOM (excluding fellow-eye wet AMD**)</td>
<td>4%</td>
<td>73%</td>
<td>2</td>
</tr>
</tbody>
</table>


**Note: Patient groups exclude patients with fellow-eye wet AMD in the analysis. Data as of August 24, 2017

*According to the Sunness et al study, 27% of GA patients have fellow-eye wet AMD
Post hoc analysis of patients with wet AMD conversions

**mITT, Observed Descriptive**

Sample size for Sham-Dry includes all subjects who did not develop wet AMD from mITT population. Sample size for all other groups includes subjects who had all images up to 12 months (i.e. Baseline, month 2, month 6 and month 12). Data as of August 24, 2017.
GA growth notably reduced in patients that converted to wet AMD

**Sham group**
Sham injections

**Active group 1**
APL-2 injections every other month

**Active group 2**
APL-2 injections every month

Lesion growth (mm)

- **2 months**
  - N=1
  - Sham group: 0.361
  - Active group 1: 0.274
  - Active group 2: 0.157

- **6 months**
  - N=80
  - Sham group: 0.355
  - Active group 1: 0.361

- **12 months**
  - N=1
  - Sham group: 0.355
  - Active group 1: 0.274

**Notes:**
- N=1 indicates a single subject.
- N=80 indicates 80 subjects.
- N=6 indicates 6 subjects.
When patients with wet AMD conversions were excluded, treatment effect persisted (post hoc)

Mean (±SE) Change from Baseline in GA Lesion (mm, square-root)

<table>
<thead>
<tr>
<th>Group</th>
<th>wAMD Converter</th>
<th>Month 2</th>
<th>Month 6</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>APL-2 Monthly (n=85)</td>
<td>No (n=71)</td>
<td>67</td>
<td>59</td>
<td>58</td>
</tr>
<tr>
<td>APL-2 EOM (n=78)</td>
<td>No (n=73)</td>
<td>70</td>
<td>64</td>
<td>56</td>
</tr>
<tr>
<td>Sham-Pooled (n=81)</td>
<td>No (n=80)</td>
<td>76</td>
<td>71</td>
<td>65</td>
</tr>
</tbody>
</table>

mITT, Observed, ANOVA at Month 12. Data as of August 24, 2017
Best Corrected Visual Acuity

No differences were observed in visual outcomes between groups.
New Onset Wet AMD

Subjects with new onset exudation in study eye:
- 1% (n=1)
- 8% (n=6)
- 18% (n=15)

Legend:
- Sham Pooled
- APL-2 Every Other Month
- APL-2 Monthly
New Onset Wet AMD

<table>
<thead>
<tr>
<th>History/Presence of CNV Fellow Eye</th>
<th>Sham Pooled</th>
<th>APL-2 Every Other Month</th>
<th>APL-2 Monthly</th>
</tr>
</thead>
<tbody>
<tr>
<td>No History/Presence of CNV Fellow Eye</td>
<td>0% (n=0)</td>
<td>14% (n=4)</td>
<td>29% (n=10)</td>
</tr>
<tr>
<td>2% (n=1)</td>
<td>4% (n=2)</td>
<td>10% (n=5)</td>
<td></td>
</tr>
</tbody>
</table>
## Adverse Event Profile

<table>
<thead>
<tr>
<th>Adverse Event n (%) of subjects with events</th>
<th>APL-2 Monthly N=86</th>
<th>APL-2 Every Other Month N=79</th>
<th>Sham Pooled N=81</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular SAEs in study eye*</td>
<td>4 (4.7%)</td>
<td>2 (2.5%)</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td>Systemic (non-ocular) SAEs</td>
<td>11 (12.8%)</td>
<td>23 (29.1%)</td>
<td>16 (19.8%)</td>
</tr>
<tr>
<td>Treatment related ocular AEs in the study eye</td>
<td>21 (24.4%)</td>
<td>11 (13.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Treatment related systemic (non-ocular) AEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### Ocular SAEs

<table>
<thead>
<tr>
<th>Ocular SAEs</th>
<th>APL-2 Monthly N=86</th>
<th>APL-2 EOM N=79</th>
<th>Sham Pooled N=81</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endophthalmitis*</td>
<td>2 (2.3%)</td>
<td>1 (1.3%)</td>
<td>0</td>
</tr>
<tr>
<td>IOP increased</td>
<td>1 (1.2%)†</td>
<td>1 (1.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>1 (1.2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>0</td>
<td>0</td>
<td>1 (1.2%)</td>
</tr>
</tbody>
</table>

*2 culture positive for coagulase-negative Staphylococcus. 1 culture negative in the monthly group
†2 events in a subject
Conclusions

• APL-2 slowed growth of GA, independent of genetics
• APL-2 appeared to increase risk of new onset wet AMD
  – No adverse impact on visual outcomes
• No safety issues preclude further development