Impact of Pegcetacoplan on Progression of Nascent Geographic Atrophy in AMD

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Financial Disclosures

• **Consultant:** Amgen, Allergan, Novartis, Roche/Genentech, Merck, 4DMT, Optos, Heidelberg, Centervue

• **Research Instruments:** Optos, Heidelberg, Centervue, Nidek, Topcon, Carl Zeiss Meditec

• **Study Support** to Doheny Image Research and Reading Lab: Apellis
Disclaimer

• Pegcetacoplan (APL-2) is an investigational product

• The safety and effectiveness of pegcetacoplan have not been determined, nor has pegcetacoplan been approved by the FDA, EMA or any other regulatory authority
Pegcetacoplan (APL-2): C3 Inhibitor

**Pegcetacoplan**
44 kDa pegylated highly-selective bi-cyclic peptide prevents C3 cleavage

**APL-2**

**Classical Pathway**

- **C3**
  - **C3a**
    - **STOP**
    - **Inflammation**
  - **C3b**
    - **STOP**
    - **Inflammation**
    - **Cell removal, Antigen uptake by APCs**

**Alternative Pathway**

- **C5**
  - **C5a**
    - **STOP**
    - **Inflammation**
  - **C5b**
    - **MAC**
    - **STOP**
    - **Cell death, secretion, lysis, or proliferation**

**Lectin Pathway**

- **C3**
  - **C3a**
    - **STOP**
    - **Inflammation**
  - **C5b**
    - **MAC**
    - **STOP**
    - **Cell death, secretion, lysis, or proliferation**

Phase 2 Trial Design

Eligible Patients with Geographic Atrophy*
246 subjects at 46 sites#

Randomized 2:2:1:1

Single Masked

Pegcetacoplan (APL-2) 15mg
Monthly (n=86)

Pegcetacoplan (APL-2) 15mg
Every Other Month (n=79)

Sham Monthly (n=41)

Sham Every Other Month (n=40)

Primary Endpoint at 12 months

No study drug administered from Month 12 to 18

End of Study at 18 months

* Confirmed by the central reading center using FAF images
# Not counting the 3 satellite sites

Protocol study number, POT-CP121614 (FILLY); NCT02503332
Pegcetacoplan (APL-2) Reduced the Rate of Lesion Growth in GA Patients

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

- APL-2 Monthly (n=84)
- APL-2 EOM (n=78)
- Sham Pooled (n=80)

Primary Endpoint
Month 12

*Square root. Modified intention-to-treat (mITT) population was used for the efficacy analysis; defined as all patients who received at least 1 injection and underwent at least 1 follow-up examination at month 2 or later at which primary efficacy data were collected. 2-sided t tests at the alpha = 0.1 level

*p=0.067 vs Sham
#p=0.008 vs Sham

Protocol study number, POT-CP121614 (FILLY); NCT02503332
## Adverse Event Profile

<table>
<thead>
<tr>
<th>Adverse Event</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>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 SAEs</td>
<td>19 (22.1%)</td>
<td>24 (30.4%)</td>
<td>23 (28.4%)</td>
</tr>
<tr>
<td>Treatment related ocular AEs in the study eye</td>
<td>22 (25.6%)</td>
<td>11 (13.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Treatment related systemic AEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<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.
Earlier Endpoints for Retina Atrophy

- Therapeutic trials for geographic atrophy are focused on the end-stage (complete RPE and outer retinal atrophy or cRORA)

- Earlier endpoints in the atrophy pathway have been defined: incomplete RPE and outer retinal atrophy (iRORA) or nascent GA (subset of iRORA without CNV)

Definition of iRORA

MUST HAVE ALL 3 of the following:

- Some hypertransmission must be present, but often discontinuous
- Some irregularity of RPE+/-BL complex
- Detectable photoreceptor degeneration, signs of which can include “wedge”, “subsidence”

- CANNOT fulfill all criteria for cRORA
Corradetti et al. (under review)

41 AMD subjects with incident iRORA followed over 24 months

Kaplan-Meier Analysis

90% of new iRORA lesions progressed to cRORA by 24 months
Post hoc Analysis: Objective

To investigate progression of nascent GA outside the GA area in patients that participated in the FILLY trial
Post hoc Analysis: *Methods*

• Included subjects that received all study treatment through Month 12 and did not develop exudative AMD:
  – Pegcetacoplan monthly (n=42)
  – Sham (n=69)

• Masked readers evaluated OCT scans outside a 500-micron perimeter from the GA border at Baseline, Month 6 and Month 12

• The following features were assessed according to CAM classification*:
  – Progression from iRORA to cRORA
  – Progression from large drusen (≥ 40 microns height) to iRORA and/or cRORA

* Sadda et al. Ophthalmology 2018;125:537-548
Post hoc Analysis: Methods
Post hoc Analysis: *Methods*

Drusen, criteria for iRORA not met

iRORA

cRORA criteria just met, RPE defect measures over 250µm
# Post hoc Analysis: Results

## Baseline Characteristics

<table>
<thead>
<tr>
<th>GA lesion size, mean, mm² (SD)</th>
<th>Pegcetacoplan Monthly (n=42)</th>
<th>Sham Injections (n=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8.05 (3.79)</td>
<td>8.31 (4.15)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Presence of large drusen*, n (%)</th>
<th>Pegcetacoplan Monthly (n=42)</th>
<th>Sham Injections (n=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>33/41 (81%)</td>
<td>49/66 (74%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Presence of iRORA*, n (%)</th>
<th>Pegcetacoplan Monthly (n=42)</th>
<th>Sham Injections (n=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>19/41 (46%)</td>
<td>36/66 (55%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lesion location:</th>
<th>Pegcetacoplan Monthly (n=42)</th>
<th>Sham Injections (n=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Foveal</td>
<td>27 (64%)</td>
<td>40 (58%)</td>
</tr>
<tr>
<td>• Extrafoveal</td>
<td>15 (36%)</td>
<td>29 (42%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lesion focality:</th>
<th>Pegcetacoplan Monthly (n=42)</th>
<th>Sham Injections (n=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Unifocal</td>
<td>13 (31%)</td>
<td>24 (35%)</td>
</tr>
<tr>
<td>• Multifocal</td>
<td>29 (69%)</td>
<td>45 (65%)</td>
</tr>
</tbody>
</table>

*Evaluable data at baseline:
PM - n=41; S - n=66
Post hoc Analysis: Results
Progression from iRORA

- Lower rate of progression (39%) from iRORA to cRORA in pegcetacoplan group compared to sham group
- Sham group 1.64 times more likely to progress to cRORA

Pearson Chi-Square:
Month 6 - P=0.08; Month 12 - P=0.02
Relative risk:
Month 12 - 0.61 (0.37-1.00)

Data on File
Post hoc Analysis: Results
Progression from Large Druse

Progression from Large Druse to iRORA or cRORA

- Relatively fewer progression events at M12 in pegcetacoplan group
- Trend suggests continued progression after M6 in sham group but not in pegcetacoplan group

Pearson Chi-Square:
Month 6 - P=0.65; Month 12 - P=0.31

3 subjects converted to cRORA at Month 12
In the FILLY trial, treatment with pegcetacoplan has shown a reduction in the progression of GA as measured by FAF.

This post hoc analysis demonstrated that patients receiving monthly pegcetacoplan had a lower rate of progression from nascent GA to GA compared to sham as assessed by OCT scans outside the GA area.

This study provides evidence to further explore the potential of pegcetacoplan for earlier intervention in the course of GA.
Global Phase 3 Program

Patients with Geographic Atrophy Secondary to AMD*
600 subjects at ~200 sites globally in 2 studies

Randomized 2:2:1:1

Double Masked

Pegcetacoplan (APL-2) 15mg Monthly

Pegcetacoplan (APL-2) 15mg Every Other Month

Sham Monthly

Sham Every Other Month

Primary Endpoint at 12 months
Change in total area of GA lesions based on FAF

End of Study at 24 months

Protocol study number, APL-2 303 (DERBY); NCT03525600
Protocol study number, APL-2 304 (OAKS); NCT03525613
Thank You