Phase 1 Study of Intravitreal Gene Therapy with ADVM-022 for Neovascular Age-related Macular Degeneration (OPTIC Trial Cohort 1)

Charles C Wykoff, MD, PhD
Director of Research, Retina Consultants of Houston
– On behalf of the OPTIC investigators –
Disclosures

- CCW: Acuela (C); Adverum (C, R); Aerie Pharmaceuticals (R); Aerpio (C, R); Alimera Sciences (C); Allegro (C); Allergan (C, R); Apellis (C, R); Bayer (C); Chengdu Kanghong (C, R); Clearside Biomedical (C, R); DORC (C); EyePoint (C); Gemini Therapeutics (R); Genentech/Roche (C, R); Graybug Vision (R); IONIS Pharmaceuticals (R); Iveric Bio (C, R); Kodiak (C, R); Neurotech (R), Novartis (C, R); ONL Therapeutics (C); Opthea (R); Outlook Therapeutics (R); Oxurion (C); PolyPhotonix (C); Recens Medical (C, R); Regeneron (C, R); Regenxbio (C, R); Samsung (R), Santen (C, R); Takeda (C).
High Treatment Burden Associated with Frequent Injections

Injection Frequency for Optimal Outcomes Often Not Realized in Real-world

37,021 Eyes of 30,106 US Patients Receiving Routine Intravitreal Anti-VEGF Therapy Over 12 Months

Development Approach to Deliver Long-term Efficacy

Gene therapy
Establish an intraocular biofactory to produce an anti-VEGF agent

BCVA, best-corrected VA; ETDRS, Early Treatment Diabetic Retinopathy Study VA, visual acuity; VEGF, vascular endothelial growth factor

Wykoff CC. Retina Society; Sept 13, 2018, San Francisco, CA
ADVM-022: Adeno-Associated Virus Gene Therapy Vector Designed For Delivery by Intravitreal Injection

**AAV.7m8 capsid**

Capsid engineered from wild-type AAV2 by directed evolution and screened for highly efficient retinal transduction following IVT injection

**Promoter**

Aflibercept expression cassette

**Aflibercept**

Strong, ubiquitous promoter designed for robust protein expression

**Codon-optimized cDNA**

Target retinal cell expresses aflibercept

Grishanin, R et al. Mol Ther 2019;27:118–29

IVT, intravitreal
Intravitreal Injection of AAV.7m8 Results in Robust Cellular Transduction and Protein Expression in the Eye

• Advanced AAV.7m8 vector developed using directed evolution to:
  – enable efficient intravitreal delivery\(^1,3\)
  – increase transduction of retinal cells\(^1,3\)
  – increase protein expression\(^1\)

• Protein expression in NHPs:
  – photoreceptors, ganglion cells\(^1–3\)
  – bipolar cells, Müller cells, optic nerve\(^2\)
  – ciliary epithelium, iris pigment epithelium\(^2\)

Preclinical NHP Data Demonstrate Long-Term Sustained Aflibercept Levels Comparable to Aflibercept Bolus Injection

Two studies: Stable long-term protein expression up to 21 and 30 months after single ADVM-022 IVT injection

Vitreous aflibercept, µg/mL

0 0.1 1 10

0 5 10 15 20 25 30

Time, months

21 days post-bolus aflibercept*

n=1 animal, 2 eyes¹

n=3 animals, 6 eyes²

38 days post-bolus aflibercept*

IVT ADVM-022

*Time after IVT injection of bolus aflibercept protein (1.2mg/eye; separate study) when similar aflibercept levels were observed in NHPs

NHP, non-human primate

2. Grishanin, R Ann Congress Eur Soc Gene Cell Ther; 2018, Lausanne, Switzerland
ADVM-022 Aflibercept is Functionally Active and Suppresses Laser-induced CNV in Primates

ADVM-022 given 13 months prior to laser-induced CNV is as effective as aflibercept administered at the time of laser

Vehicle: 40%  
Aflibercept: 5%*  
ADVM-022: 6%*

*\( p<0.0001 \) (Fisher’s exact test versus vehicle)

CNV, choroidal neovascularization

Grishanin, R et al. Mol Ther 2019;27:118–29
OPTIC: Phase 1, Two-year Multicenter Study of ADVM-022 in Neovascular AMD

- **Primary objective**
  - Assess the safety and tolerability of a single IVT injection of ADVM-022

- **Secondary objectives**
  - Evaluate vision (BCVA)
  - Evaluate anatomy (SD-OCT)
  - Assess the need for rescue therapy

**Day 1:** Baseline assessment

**Day –15 to –7:** Aflibercept

**Day 1:** ADVM-022

**24-week safety and efficacy assessment**

**52-week safety and efficacy assessment**

**Follow-up**

Weeks: 4 8 12 16 20 24 52 104

**Oral steroid prophylaxis***: Cohort 1 (6x10^{11} vg/eye, n=6) and Cohort 2 (2x10^{11} vg/eye, n=6)

**Steroid eye drops prophylaxis****: Cohort 3 (2x10^{11} vg/eye, n=9) and Cohort 4 (6x10^{11} vg/eye, n=9)

**Patients receive rescue aflibercept (2mg IVT) if any of the following criteria are met:**

1. Loss of ≥10 letters in BCVA from baseline that is attributed to intraretinal or subretinal fluid observed by the investigator
2. Increase in central subfield thickness >75μm from baseline
3. Presence of vision-threatening hemorrhage due to AMD

*S*ubjects received prophylaxis of 60mg oral prednisone for 6 days starting at Day –3 followed by 7-day taper.

**S**ubjects receive prophylaxis of QID difluprednate eye drops for 3 weeks starting at Day 1 followed by a 3-week taper.

BCVA, best-corrected visual acuity; IVT, intravitreal therapy; SD-OCT, spectral domain optical coherence tomography; QID, 4x/day

**NCT03748784**
Study Population Previously Required Frequent Injections to Maintain Vision

<table>
<thead>
<tr>
<th>Baseline Characteristics of Cohort 1 (n=6 patients)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>79.0</td>
</tr>
<tr>
<td>Mean time since nAMD diagnosis, years</td>
<td>3.3</td>
</tr>
<tr>
<td>Mean number anti-VEGF injections since initial diagnosis (range)</td>
<td>35.3 (7–109)</td>
</tr>
<tr>
<td>Mean number anti-VEGF injections in 12 months prior to ADVM-022</td>
<td>9.2</td>
</tr>
<tr>
<td>Mean BCVA study eye, ETDRS letters</td>
<td>65.8</td>
</tr>
<tr>
<td>Approximate Snellen equivalent</td>
<td>20/50</td>
</tr>
<tr>
<td>Mean CST study eye, µm</td>
<td>369.2</td>
</tr>
</tbody>
</table>

BCVA, best corrected visual acuity; CST, central subfield thickness; ETDRS, Early Diabetic Retinopathy Study nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor
December 1, 2019
Update of OPTIC Cohort 1

Presentation includes:

- Safety
- Time-course and management of intraocular inflammation
- Mean change in BCVA and CST
- Individual patient OCTs/BCVA/CST at most recent visit
- Anti-VEGF rescue requirement

<table>
<thead>
<tr>
<th>Data Through December 1, 2019 (n=6)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up, weeks</td>
<td>44.0</td>
</tr>
<tr>
<td>Follow-up (min, max), weeks</td>
<td>40, 52</td>
</tr>
</tbody>
</table>

BCVA, best-corrected visual acuity; CST, central subfield thickness; VEGF, vascular endothelial growth factor.
Cohort 1 Safety Results Through December 1, 2019

- No ADVM-022- or procedure-related serious adverse events (SAEs)
- No ADVM-022-related systemic adverse events
- No adverse events met criteria for dose-limiting toxicity
- ADVM-022-related adverse events have been mild (75%) to moderate (25%)
  - Low-grade inflammation commonly reported
  - No vasculitis, retinitis, or choroiditis
- One unrelated ocular SAE
  - Spontaneous, pseudophakic* retinal detachment
  - Surgically repaired and remains under follow-up

*Previous cataract extraction and artificial lens implantation
**Cellular Inflammation Assessed by Slit Lamp Examination**

*Cohort 1: Low Grade and Responsive to Topical Steroids*

**Aqueous cell grade categories are based on the Standardization of Uveitis Nomenclature (SUN) criteria: Jabs, DA et al. J Ophthalmol. 2005;140:509–516**

**Vitreous cell grade categories are based on National Institutes of Health (NIH) guidelines**

Aqueous cells: 0.5+: 1-5 cells 1+: 6-15 cells 2+: 16-25 cells 3+: 26-50 cells 4+: >50 cells

Vitreous cells: 0.5+: 1-10 cells 1+: 11-20 cells 2+: 21-30 cells 3+: 31-100 cells 4+: >100 cells; rare cells are captured as 0.5+ for this analysis
Cohort 1 Update: Additional Follow-up Data

<table>
<thead>
<tr>
<th>Outcomes Through December 1, 2019 (Median 44 Weeks Follow-up)*</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BCVA change from baseline, ETDRS letters</td>
<td>−1.0</td>
</tr>
<tr>
<td>BCVA change from baseline (min, max), ETDRS letters</td>
<td>−7, +7</td>
</tr>
<tr>
<td>Mean CST change from baseline, µm</td>
<td>−25.5</td>
</tr>
<tr>
<td>CST change from baseline (min, max), µm</td>
<td>−117, +32</td>
</tr>
<tr>
<td>Total number of rescue injections, n</td>
<td>0</td>
</tr>
</tbody>
</table>

*BCVA and CST for patient 4 with retinal detachment (unrelated to study treatment) use last observations prior to detachment (week 36)

BCVA, best-corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study
Anatomic Improvements and BCVA Maintained
Additional Follow-up Through December 1, 2019

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline OCT</strong></td>
<td><img src="Image1" alt="Baseline OCT" /></td>
<td><img src="Image2" alt="Baseline OCT" /></td>
<td><img src="Image3" alt="Baseline OCT" /></td>
</tr>
<tr>
<td><strong>Latest OCT</strong></td>
<td><img src="Image4" alt="Latest OCT" /></td>
<td><img src="Image5" alt="Latest OCT" /></td>
<td><img src="Image6" alt="Latest OCT" /></td>
</tr>
<tr>
<td><strong>BCVA Change</strong></td>
<td>+7</td>
<td>−6</td>
<td>−7</td>
</tr>
<tr>
<td>from Baseline, ETDRS letters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CST change</strong></td>
<td>+32</td>
<td>−29</td>
<td>−55</td>
</tr>
<tr>
<td>from Baseline, µm</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; IVT, intravitreal therapy; OCT, optical coherence tomography
### Anatomic Improvements and BCVA Maintained

*Additional Follow-up Through December 1, 2019*

<table>
<thead>
<tr>
<th>Patient 4: 44 Weeks* Post-ADVM-022</th>
<th>Patient 5: 40 Weeks Post-ADVM-022</th>
<th>Patient 6: 40 Weeks Post-ADVM-022</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline OCT</strong></td>
<td><img src="image1" alt="Baseline OCT Image" /></td>
<td><img src="image2" alt="Baseline OCT Image" /></td>
</tr>
<tr>
<td><strong>Latest OCT</strong></td>
<td><img src="image4" alt="Latest OCT Image" /></td>
<td><img src="image5" alt="Latest OCT Image" /></td>
</tr>
<tr>
<td><strong>BCVA Change from Baseline, ETDRS letters</strong></td>
<td>+5*</td>
<td>-2</td>
</tr>
<tr>
<td><strong>CST change from Baseline, µm</strong></td>
<td>−117*</td>
<td>+4</td>
</tr>
</tbody>
</table>

*BCVA, CST and OCT images for patient with retinal detachment (unrelated to study treatment) uses last observations prior to detachment (week 36)

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study

IVT, intravitreal therapy; OCT, optical coherence tomography
No Anti-VEGF Injections Required After ADVM-022
Median 44 Weeks Follow-up

Patient # | Frequent anti-VEGF injections prior to ADVM-022 | No rescue injections after ADVM-022
---|---|---
1 |  |  |
2 |  |  |
3 |  |  |
4 |  |  |
5 |  |  |
6 |  |  |

- | Bevacizumab | Afibercept | Ranibizumab | No rescue injection given

*Time relative to ADVM-022 injection date
OPTIC Cohort 1 Conclusions
As of December 1, 2019 (Median of 44 Weeks; Range 40–52 Weeks)

- Mean BCVA and CST maintained
- Low-grade ocular inflammation responsive to steroid eyedrops
  - Cohorts 3 and 4 utilize 6-week prophylactic steroid eye drop regimen
- Zero rescue injections required
- ADVM-022 has the potential to greatly reduce anti-VEGF injection burden in neovascular AMD

AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; CST, central subfield thickness; VEGF, vascular endothelial growth factor
ADVM-022 Outlook

- **OPTIC (nAMD)**
  - Cohort 2 completed enrollment
  - Cohort 3 enrollment open
    - ADVM-022 ($2 \times 10^{11}$ vg/eye) with steroid eye drops prophylaxis
  - Cohort 4 enrollment Q1 2020
    - ADVM-022 ($6 \times 10^{11}$ vg/eye) with steroid eye drops prophylaxis
  - Cohort 1 52-week data H1 2020
  - Cohort 2 24-week data: Angiogenesis, Exudation and Degeneration
    February 8, 2020

- IND submission in diabetic retinopathy H1 2020 and study start H2 2020
ADVM-022 Acknowledgments

Investigators, study teams and participants

- David Boyer MD
- Brandon Busbee MD
- Brian Joondeph MD
- Arshad Khanani MD
- James Major MD
- Dante Pieramici MD
- Carl Regillo MD
- Charles Wykoff MD, PhD
- Mehdi Gasmi PhD
- Szilard Kiss MD
- Aaron Osborne MBBS
- Carol Hoang, PharmD
- Adam Turpcu, PhD

Bakersfield, CA  
Beverly Hills, CA  
Golden CO  
Reno NV  
Philadelphia, PA  
Nashville, TN  
Woodlands, TX  
Houston, TX  
OIRRC, Sunnyvale, CA  
Independent reading center