Intravitreal ADVM-022 Gene Therapy for Wet AMD: Overview of 2-Year Results with Detailed Analysis of Fluid Volatility and Outer Retinal Integrity

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Disclosures

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OPTIC Study: 2-Year Safety and Efficacy of ADVM-022 for nAMD



 Primary Objective Assess the safety and tolerability of a single IVT injection of ADVM-022 		 Secondary Objective Evaluate vision maintenance (BCVA) Evaluate anatomy (SD-OCT) Assess the need for supplemental therapy Evaluate effect of ADVM-022 on presence of IRF & SRF 		
Day –15 to –7: Day 1: ADVM-022	24-Wee Efficacy	k Safety and Assessment	52-Week Safety and Efficacy Assessment	104-Week Safety and Efficacy Assessment
Baseline Assessment Tre	atment Evaluation	Treatment E	valuation Treatme r	nt Evaluation Extensio Study

	Prophylaxis Steroid Regimen
Cohort 1 (n=6) 6 x 10 ¹¹ high dose	Oral*, 13d
Cohort 2 (n=6) 2 x 10 ¹¹ low dose	Oral*, 13d
Cohort 3 (n=9) 2 x 10 ¹¹ low dose	Eye Drops**, 6 wks
Cohort 4 (n=9) 6 x 10 ¹¹ high dose	Eye Drops**, 6 wks

Supplemental Aflibercept (2 mg IVT) Criteria:

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

*Subjects received prophylaxis of 60 mg oral prednisone for 6 days starting at Day –3 followed by 7-day taper. **Subjects received prophylaxis of QID difluprednate eye drops for 3 weeks starting at Day 1 followed by a 3-week taper. Final analysis includes all participants regardless of baseline neutralizing antibody titer.

AAV, adeno-associated virus; AMD, age-related macular degeneration; BCVA, best corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; IVT,

intravitreal therapy; QID, four times daily; SD-OCT, spectral domain optical coherence tomography; NCT03748784.

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ADVM-022 OPTIC Study Baseline Characteristics



Baseline Characteristics	2x10 ¹¹ vg/eye (N=15)	6x10 ¹¹ vg/eye (N=15)
Mean (range) Age, Years	78.4 (65–90)	79.5 (62–88)
Mean (range) Years Since nAMD Diagnosis	3.6 (0.5–8.0)	3.8 (0.2–10.6)
Mean (range) Number anti-VEGF Injections Since Initial Diagnosis [*]	28.5 (4–70)	30.7 (2–109)**
Mean (range) Annualized anti-VEGF Injections 12 Months Prior to ADVM-022	10.0 (8.0–12.9)	9.8 (6.3–13.4)**
Mean (range) BCVA, ETDRS Letters Approximate Snellen Equivalent	65.4 (53–75) 20/50	65.3 (54–77) 20/50
Mean (range) CST, μm	407.1 (235–857)	386.8 (255–561)

*Not including the mandated aflibercept at Screening; **Excluding participant #2 with incomplete prior anti-VEGF data;

BCVA, best corrected visual acuity: CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; NAbs, neutralizing antibodies; nAMD, neovascular age-related macular degeneration;

VEGF, vascular endothelial growth factor

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ADVM-022 OPTIC Study Safety Summary



- Despite the short duration of prophylactic corticosteroid therapy, ADVM-022 was generally well tolerated, with the most common AE of dose-dependent, mild to moderate* inflammation that was responsive to topical corticosteroids
 - At study completion, inflammation in the 2x10¹¹ dose group resolved in all participants and no participants required corticosteroid therapy
- Across all cohorts, most ADVM-022-related ocular AEs were mild (83.7%) to moderate (15.6%)
- The most commonly reported ocular AE was anterior chamber cell
- Two ADVM-022 related SAEs were reported: uveitis (responsive to topical corticosteroids) and dry AMD
- No vasculitis, retinitis, choroiditis, vascular occlusions or endophthalmitis
- No clinically relevant low IOP events observed at either dose

AC, aqueous cells; AE, adverse event; SAE, serious adverse event; VC, vitreous cells.

*Mild inflammation: trace, 0.5+, 1+ and 2+ anterior chamber cell/flare, or trace, 0.5+, 1+ and 2+ vitreous cells; moderate inflammation: +3 anterior chamber cell/flare, or 3+ vitreous cells,

severe inflammation: +4 anterior chamber cell/flare, or 4+ vitreous cells

ADVM-022 Maintains or Improves BCVA and CST Through 2 Years





Continuous Aflibercept Protein Expression Following ADVM-022 Substantially Reduces Annualized Anti-VEGF Injections



*Modeled based on Do et al. Retina 2020; 40:643-647.

** Participant received supplemental aflibercept injections

Protocol amendment for aqueous sample collection for participants that consented. To isolate the effect of ADVM-022, samples that were collected within 2 months of supplemental aflibercept are not shown. Annualized rate (Prior) = (number of IVTs in 12 months prior to ADVM-022) / (days from the first IVT in the past 12 months to ADVM-022 / 365.25).

Annualized rate (Post) = (numbers of aflibercept IVTs since ADVM-022) / (days from ADVM-022 to the last study follow-up / 365.25).

VEGF, vascular endothelial growth factor.

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IRF, SRF, SRM, and EZ Integrity are All Important Predictors of Visual Function

- The presence of retinal fluid has been associated with poorer long-term outcomes in nAMD patients
 - This link to worsening BCVA has been most strongly associated with intraretinal fluid (IRF) in particular
- Greater fluctuations in retinal fluid have been linked to macular atrophy and fibrosis
- Presence of subretinal material (SRM) on OCT has been associated with poorer preservation of the ellipsoid zone (EZ)
- EZ attenuation/loss is an indicator of photoreceptor loss in nAMD
- Better fluid control, lower levels of SRM, and EZ integrity have all been associated with improved long-term BCVA in nAMD patients
- Emerging therapeutics such as ADVM-022 may have a differential impact on each of these parameters

Volumetric Fluid Assessment



Methods

- The following analyses examine the impact of a single IVT injection of ADVM-022 gene therapy on IRF, SRF, SRM, and outer retinal integrity in the OPTIC Study
- Machine Learning-Enhanced multi-layer segmentation and feature extraction with expert reader validation was performed at the Tony and Leona Campane Center for Excellence in Image-Guided Surgery and Advanced Imaging Research, Cole Eye Institute, Cleveland Clinic
- Works on multiple OCT devices
- Built on foundation of over 500,000 annotated B-scans



Single IVT Injection of ADVM-022 at 2x10¹¹ Dose: 80% Reduction in Mean SRF Volume from Baseline to 2 Years



Mean SRF Volume (by Dose)



Single IVT Injection of ADVM-022 at 2x10¹¹ Dose: 190% Increase in Percentage of Participants with Dry SRF from Baseline to 2 Years



Percentage of Participants with Dry* SRF (by Dose)

Percentage with Dry SRF at Baseline Percentage with Dry SRF at Week 104



Single IVT Injection of ADVM-022 at 2x10¹¹ Dose: 99% Reduction in Mean IRF Volume from Baseline to 2 Years





Mean IRF Volume (by Dose)

Single IVT Injection of ADVM-022 at 2x10¹¹ Dose: 68% Increase in Percentage of Participants with Dry IRF from Baseline to 2 Years



Percentage of Participants with Dry* IRF (by Dose)

Percentage with Dry IRF at Baseline
Percentage with Dry IRF at Week 104



Single IVT Injection of ADVM-022 at 2x10¹¹ Dose: 69% Reduction in Mean SRM Volume from Baseline to 2 Years



Mean SRM Volume (by Dose)



it IRF 10 10. SRF Fluid Thickness ... Foveal B-Scan Fluid Overlay -- Contract ANT CARE OF WEEK 12 28 Weeks Since Start of Study Period -30 -15 48 60 80 96 -2 16

ADVM-022

OPTIC Patient Case: Cohort 3 (2x10¹¹ vg/eye)

Patient Case – Cohort 3 (2x10¹¹ vg/eye): Change in Intraretinal and Subretinal Fluid Volume (mm³) Over 2 years







OPTIC Patient Case: Cohort 2 (2x10¹¹ vg/eye)



Weeks Since Start of Study Period

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Patient Case – Cohort 2 (2x10¹¹ vg/eye): Change in Intraretinal Fluid, Subretinal Fluid, and Subretinal Material Volume (mm³)



Outer Retinal Integrity Assessment

Ellipsoid Zone Integrity is an Important Predictor of Visual Function

- In addition to reductions in retinal fluid and SRM, another important marker of treatment response includes ellipsoid zone (EZ) integrity:
 - EZ attenuation may be an indicator of photoreceptor loss in nAMD
 - % total attenuation refers to the % of the EZ-RPE total with a thickness of 0 μm on an *en face* map
 - % partial attenuation refers to the % of the EZ-RPE total with a thickness <20 µm on an *en face* map
- Improvements in EZ integrity have consistently been associated with improvements in BCVA



Total attenuation



Partial attenuation



Integrity maintenance

Machine Learning Enhanced Compartmental Segmentation





512 × 128 A-scans Cirrus HD-OCT (Zeiss)





Outer Retinal Mapping



3D reconstruction of macular cube

En face view of normative EZ mapping

Quantitative retinal parameters include:

- ➢ EZ-RPE CST
- EZ-RPE volume
- Percentage of EZ-RPE total attenuation (i.e., thickness of 0 µm) and partial attenuation (i.e.,< 20 µm) on *en face map*)

Partial EZ Attenuation Stable Over Time in Both Dose Groups in Treatment-Experienced Patients. Positive Indicator for BCVA Preservation





Total EZ Attenuation Stable Over Time in Both Dose Groups in Treatment-Experienced Patients. Positive Indicator for BCVA Preservation





Single IVT Injection of ADVM-022: Increase in EZ Preservation within Central Subfield from Baseline to 2 Years





ADVM-022 6x10¹¹ vg/eye

100% 93.3% 84.6% 80% 60% 40% 20% 15.4% 6.7% 0% Partial or Total attenuation Integrity Maintenanace ■ Baseline ■ Year 2

ADVM-022 2x10¹¹ vg/eye

Eyes with Maintained EZ within the Central Subfield have Best **BCVA Outcomes**





Mean BCVA and EZ Maintenance Following ADVM-022 (6x10¹¹ and 2x10¹¹)



- A single, in-office IVT administration of ADVM-022:
 - Resulted in stable, persistent aflibercept expression through 3 years
 - Maintained BCVA at 2 years while markedly reducing anti-VEGF treatment burden
 - Meaningfully reduced SRF, IRF, and SRM volume and demonstrated EZ preservation, all of which may result in better long-term visual outcomes
- Limitations of this analysis include small sample size
- ADVM-022 was generally well tolerated in OPTIC. Inflammation was dose-dependent, mild to moderate, and responsive to topical corticosteroids
- The results from the OPTIC study support the further development of ADVM-022 for nAMD
 - The Phase 2 LUNA study is now enrolling and is evaluating the 2x10¹¹ vg/eye dose as well as a lower 6x10¹⁰ vg/eye dose. The impact of fluid volatility on overall outcomes will be further assessed in this study.

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