Phase 1 Study of Intravitreal (IVT) Gene Therapy with ADVM-022 for Neovascular AMD (OPTIC Trial): The Role of Neutralizing Antibodies (NAbs)

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Poster # 306

Background

- Neovascular age-related macular degeneration (nAMD) is a chronic degenerative disease affecting the macula and is the most common cause for vision loss in adults aged 60 years or older.[1,2]
- In nAMD, the upregulation of vascular endothelial growth factor (VEGF) in the retina contributes to choroidal neovascularization (CNV), a process characterized by the development of abnormal blood vessels that can leak fluid and blood and damage the photoreceptors and retinal pigment epithelium.[1-3]
- The current standard of care for treating nAMD consists of frequent repeated administration of VEGF inhibitors, which can present a significant burden to patients, caregivers, and physicians.[3,4]
- Gene therapy is a promising approach that enables long-term delivery of a therapeutic transgene product following a single injection.[4]

ADVM-022 is a novel biofactory approach to gene therapy designed for continuous delivery of aflibercept after a single intravitreal injection

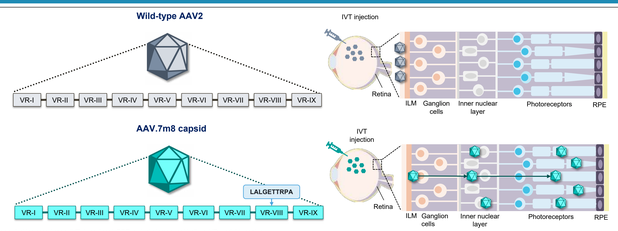
Figure 1. Structure of AAV.7m8 capsid versus wild-type AAV2

ADVM-022[5]

- Gene therapy vector that uses AAV.7m8 capsid to deliver a transgene encoding aflibercept.

7m8 adeno-associated virus (AAV.7m8) capsid[5-8]

- Engineered variant of AAV2 with a 10-amino-acid (LALGETTRPA) loop insertion.
- Modification allows the vector to bypass the inner limiting membrane to efficiently transduce and deliver transgenes to target retinal cells.



ILM, inner limiting membrane; IVT, intravitreal; RPE, retinal pigment epithelium; VR, variable region.

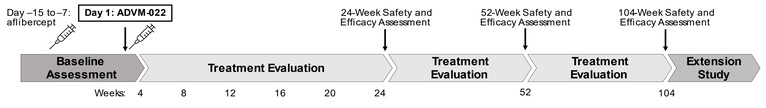
Purpose

- Previously reported data from the phase 1 OPTIC study (NCT03748784) of ADVM-022 (AAV.7m8-aflibercept) in nAMD patients demonstrated that a single intravitreal (IVT) injection of gene therapy that results in durable intraocular aflibercept expression can reduce the need for frequent anti-VEGF injections and improve visual and anatomical outcomes.[9,10]
- The potential impact of baseline levels of neutralizing antibodies (NAbs) to AAV.7m8 on efficacy and safety outcomes are reported.

Study Design and Methods

- OPTIC is an open-label, multicenter, dose-ranging study designed to evaluate the safety, tolerability, and efficacy of a single IVT injection of ADVM-022 in treatment-experienced nAMD patients (N=30; Figure 2).
- OPTIC included 4 cohorts which varied by dose and prophylactic steroid regimen (n=6 each in Cohort C1 and C2; n=9 each in C3 and C4; Figure 2).
- Participants received supplemental aflibercept if they met any of the following criteria: 1) 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 (CST) >75 µm from baseline; 3) Presence of vision-threatening hemorrhage due to AMD.

Figure 2. OPTIC Study Design



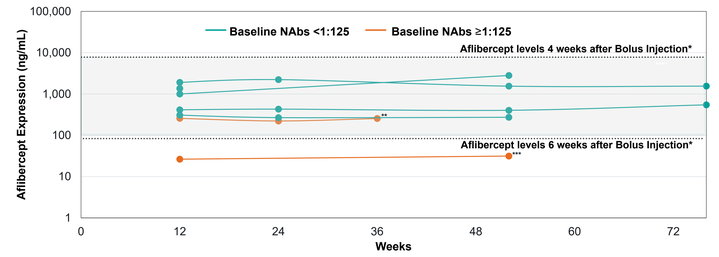
Cohort	Dose	Prophylactic steroid regimen
1	$6x10^{11}$	Oral, 13 days
2	$2x10^{11}$	Oral, 13 days
3	$2x10^{11}$	Eye drops, 6 weeks
4	$6x10^{11}$	Eye drops, 6 weeks

- A qualitative cell-based assay was used to detect anti-AAV antibodies with the capacity to neutralize AAV.7m8 in human serum.
- NAbs exclusion criteria were a titer level of ≥1:5 for cohort 1 and ≥1:125 for cohorts 2-4.
- The impact of baseline NAbs on treatment burden, aflibercept protein expression levels, CST fluctuations, and safety outcomes was evaluated.

Results

- As of July 16, 2021, median follow-up was 104 weeks (C1 and C2), 92 weeks (C3), and 60 weeks (C4).
- In C2 through C4, 89% (8/9) of $6x10^{11}$ and 67% (10/15) of $2x10^{11}$ vg/eye participants had baseline NAb titers <1:125.
- 12 of 15 participants receiving $6x10^{11}$ and 8 of 15 receiving $2x10^{11}$ vg/eye ADVM-022 remained supplemental anti-VEGF injection-free.
- Participants with NAb titers <1:125 at baseline showed more robust aflibercept protein expression levels compared with patients with baseline NAbs ≥1:125 (Figure 3).
- The majority of participants with NAbs titers <1:125 in the $2x10^{11}$ vg/eye group remained supplemental injection-free (Figure 4).
- The mean annualized anti-VEGF injection rate was reduced by 81% in all participants receiving $2x10^{11}$ vg/eye and 94% in participants with NAbs titers <1:125 (Figure 5).

Figure 3. Protein expression in participants receiving $2x10^{11}$ vg/eye ADVM-022

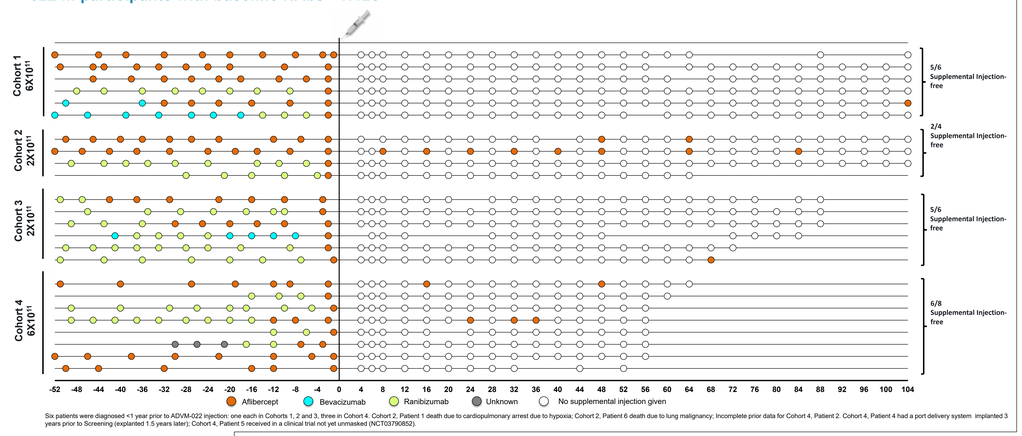


*Modeled based on Do DV, et al. *Retina*. 2020;40(4):643-647; ** Patient rescued at Week 36; *** Patient rescued at Week 24. Sample collected 28 weeks after supplemental injection.
Protocol amendment for aqueous sample collection for patients who consented. No samples available from Cohort 2. To isolate the effect of ADVM-022, samples that were collected within 2 months of supplemental aflibercept are not shown.

Safety

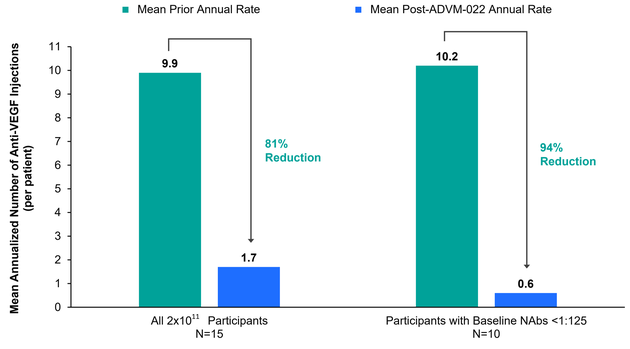
- ADVM-022 related events were mild (83%) or moderate (17%) across all cohorts.
- One serious adverse event of uveitis occurred in C1 ($6x10^{11}$ dose) and was responsive to topical corticosteroids.
- All inflammation observed at the $2x10^{11}$ dose was responsive to topical corticosteroids.
- At most recent follow-up, no participants in the $2x10^{11}$ vg/eye cohorts required any topical corticosteroids to treat inflammation.
- No correlation between NAbs titer and inflammation was observed.
- ADVM-022 continues to be well tolerated with a favorable safety profile in the nAMD population.

Figure 4. Reduction in requirement for supplemental anti-VEGF injections following a single intravitreal injection of ADVM-022 in participants with baseline NAbs <1:125



Six patients were diagnosed <1 year prior to ADVM-022 injection: one each in Cohorts 1, 2 and 3, three in Cohort 4. Cohort 2, Patient 1 death due to cardiopulmonary arrest due to hypoxia; Cohort 2, Patient 6 death due to lung malignancy; Incomplete prior data for Cohort 4, Patient 2. Cohort 4, Patient 4 had a port delivery system implanted 3 years prior to Screening (explanted 1.5 years later); Cohort 4, Patient 5 received in a clinical trial not yet unmasked (NCT03790852).

Figure 5. Reduction in annualized anti-VEGF injections in participants receiving $2x10^{11}$ vg/eye ADVM-022



Annualized rate (Prior) = (number of aflibercept 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).
A 97% reduction in annualized anti-VEGF injections was observed in the $6x10^{11}$ group.

Conclusions

- The mean annualized anti-VEGF injection rate was reduced by 81% in all participants receiving $2x10^{11}$ vg/eye ADVM-022 and 94% in participants with NAbs titers <1:125, suggesting participants with baseline NAbs to AAV.7m8 <1:125 were more likely to demonstrate robust aflibercept protein expression and were less likely to require supplemental anti-VEGF injections.
- Both doses of ADVM-022 were well tolerated, with the $2x10^{11}$ vg/eye dose requiring less topical corticosteroid therapy to alleviate inflammation.
- Baseline NAbs were not associated with occurrence or duration of inflammation or other safety events.
- A Phase 2 study in nAMD investigating the $2x10^{11}$ vg/eye dose and a lower $6x10^{10}$ vg/eye dose of ADVM-022 as well as new enhanced prophylactic steroid regimens is planned.

References: 1. Ammar MJ, et al. *Curr Opin Ophthalmol*. 2020;31(3):215-221; 2. Khanani AM, et al. *Ophthalmol Retina*. 2020;4(2):122-133; 3. Wykoff CC, et al. *J Manag Care Spec Pharm*. 2018;24(2-a Suppl):S3-S15; 4. Guimaraes TAC, et al. *Br J Ophthalmol*. 2021;105(2):151-157; 5. Grishanin R, et al. *Mol Ther*. 2019;27(1):118-129; 6. Bennett A, et al. *J Struct Biol*. 2020;209(2):107433; 7. Dalkara D, et al. *Sci Transl Med*. 2013;5(189):189ra76; 8. Khabou H, et al. *Biotechnol Bioeng*. 2016;113(12):2712-2724; 9. Busbee BG. OPTIC study of intravitreal gene therapy with ADVM-022 for neovascular age-related macular degeneration. Presented at: ARVO; May 1-7, 2021; Virtual; 10. Khanani AM. ADVM-022 intravitreal gene therapy for neovascular AMD – Phase 1 OPTIC study. Presented at: Retina Society; September 29 – October 2, 2021; Chicago, IL, US.

Disclosures: A. Turpcu, K. Bender, M. Friedman, E. Chung, and J. Han are employees of Adverum Biotechnologies (E); S. Kiss is a consultant of Adverum Biotechnologies (C).