AAV.7m8-aflibercept Provides Long Term Protection in a Nonhuman Primate Model of Wet Macular Degeneration

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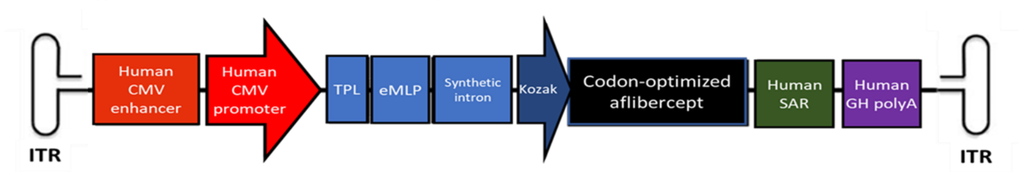
Background

- Wet age-related macular degeneration (wAMD) is the leading cause of severe vision loss in adults over 50 years old
- Vision loss results from abnormal blood vessel proliferation and leakage due to VEGF activity
- Challenging compliance
  - Need for monthly/every other month intravitreal injections of anti-VEGF therapy
  - Under-dosing results in disease progression and vision loss
- A durable delivery system for anti-VEGF therapy, overcoming compliance issues is a significant unmet medical need

Purpose

- Adverum is developing ADVM-022 as an intravitreal (IVT) gene therapy vector to treat wAMD
- ADVM-022 is an AAV.7m8 capsid vector which has been engineered for efficient transduction of the retina upon intravitreal administration
- ADVM-022 expression cassette has been optimized for robust expression of aflibercept, an approved wAMD anti-VEGF protein therapy
- The aim of the study was to assess whether a single IVT administration of ADVM-022 could deliver durable aflibercept expression to the retina, as well as long-term protection against laser-induced choroidal neovascularization in the non-human primate model of wAMD

Design of the aflibercept expression cassette



Study Design and Methods

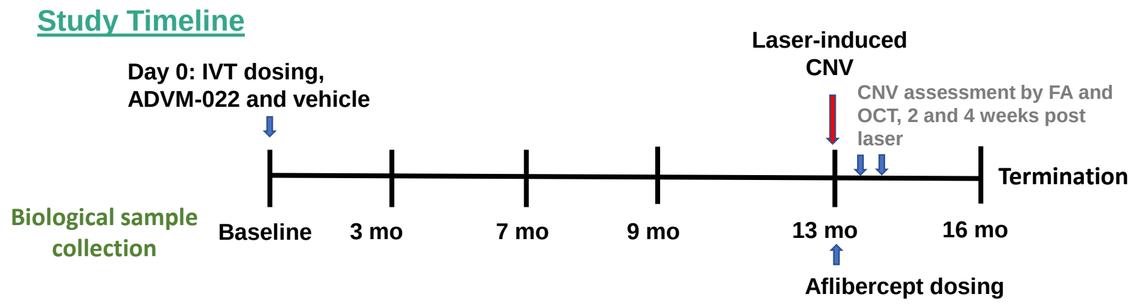
Animals: This study was conducted in adult African green monkeys (*Chlorocebus sabaeus)*
Evaluations: All eyes were examined by slit lamp biomicroscopy, fundoscopy, color fundus photography, tonometry, fluorescein angiography (FA) and OCT
Laser-induced CNV model: CNV was induced by laser photocoagulation using 9 macular laser spots in each eye
Assessment of CNV:

- CNV lesions were assessed by FA and OCT at 2 and 4 weeks post laser photocoagulation. Graded scoring of angiograms was performed in a masked fashion
- SD-OCT was used to measure laser-induced fibro-vascular complex size, by cross-sectional area analysis of the lesion

Bioanalytical analysis for aflibercept expression: Aflibercept levels in vitreous and retinal tissues were measured by ELISA specific for unbound aflibercept
Statistical methods: Graded (I-IV) scoring of laser lesions was analyzed using the Fisher's exact test. CNV complex cross-section area data were analyzed by Mann-Whitney U test

Group	Treatment	N	Dose (IVT; OU)	Treatment delivery	Laser (OU) relative to Day 0
1a	ADVM-022	2M/2F	$2x10^{12}$ vg/50µL	Day 0	13 month
1b		2M/1F	$2x10^{12}$ vg/50µL	Day 0	Not lasered
2a	Vehicle	2M/2F	50µL	Day 0	13 months
2b		2M/1F	50µL	Day 0	Not lasered
3	Aflibercept	2M/2F	1.2 mg/30µL	Day of laser	13 months

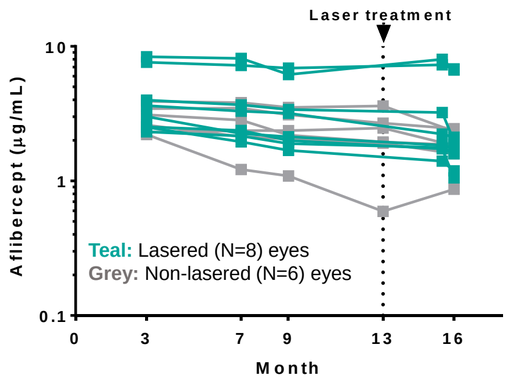
Study Timeline



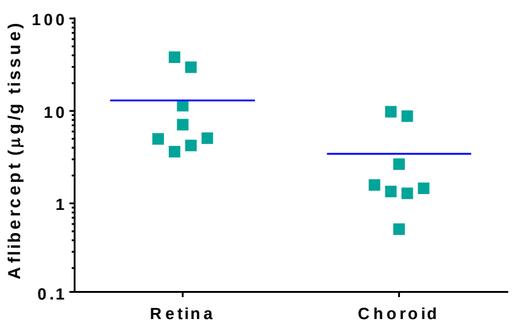
Results

IVT delivery of ADVM-022 provides stable intraocular expression of aflibercept

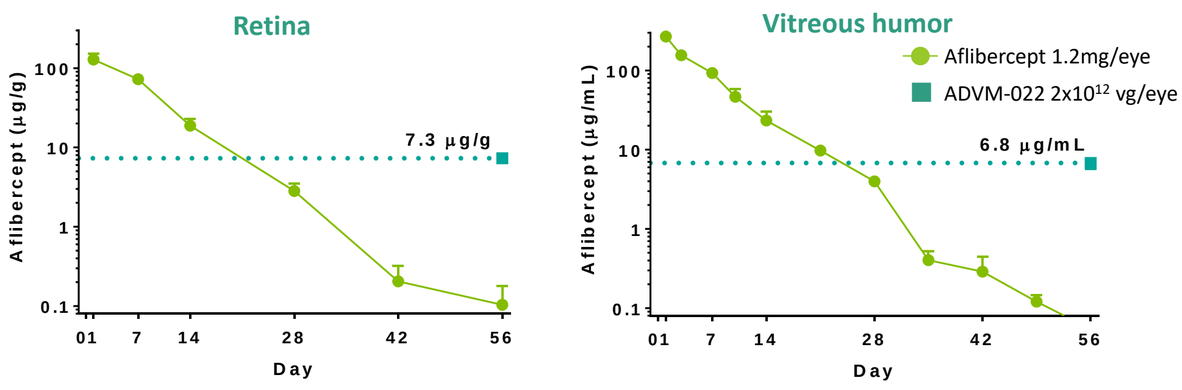
Aflibercept expression in vitreous humor of ADVM-022-treated animals



Aflibercept levels in retina and choroid 16 months post ADVM-022 delivery (N=8 eyes)

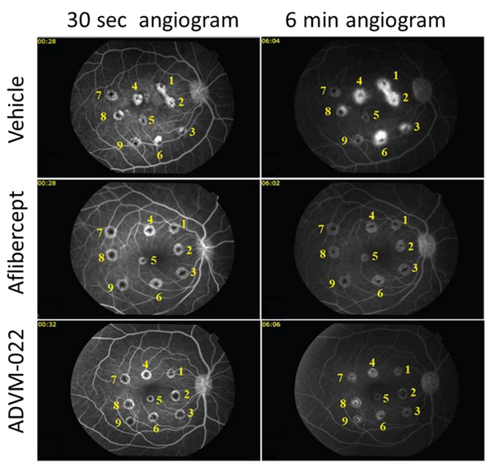


Retinal and vitreous humor levels of aflibercept 56 days post ADVM-022 vs bolus of aflibercept recombinant protein (standard of care)

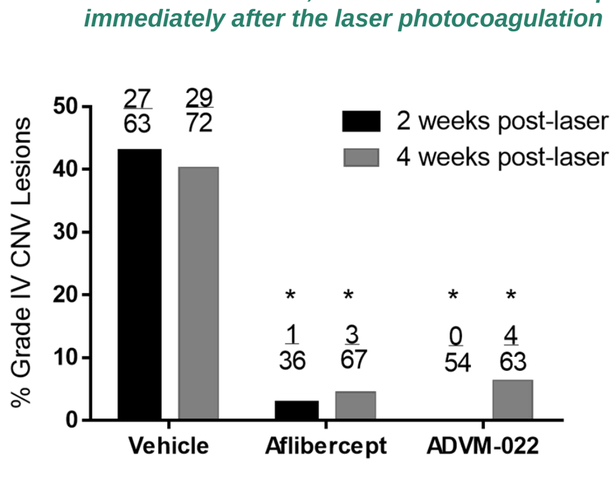


A single dose IVT ADVM-022 administered 13 mo. prior to laser significantly reduces the incidence of Grade IV CNV lesions

Representative fluorescence angiograms from vehicle-injected, aflibercept-injected or ADVM-022-injected eyes



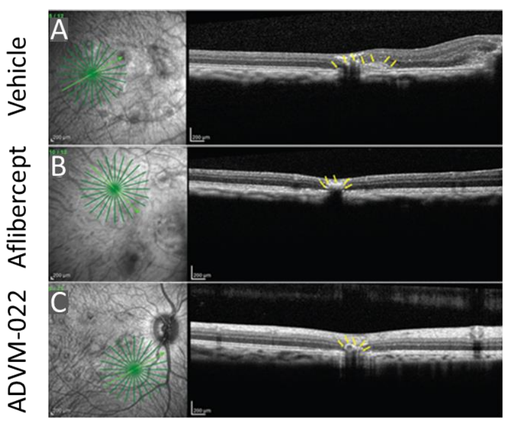
Incidence of Grade IV lesions in groups treated 13 months prior to the CNV induction with vehicle or ADVM-022, or treated with aflibercept immediately after the laser photocoagulation



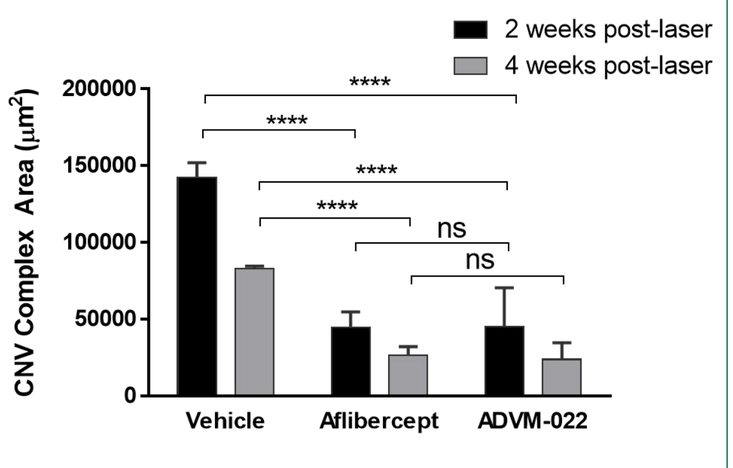
P < 0.0001 vs. vehicle, Fisher's exact test. There was no statistical difference between the ADVM-022 and aflibercept groups. Numbers on the top of bars show the absolute number of Grade IV lesions scored over the total number of assessable lesions.

A single dose of IVT ADVM-022 administered 13 mo. prior to laser significantly reduces the size of fibro-vascular CNV complexes

Representative OCT images at 4 weeks post-laser from eyes receiving vehicle (A), aflibercept (B), or ADVM-022 (C)

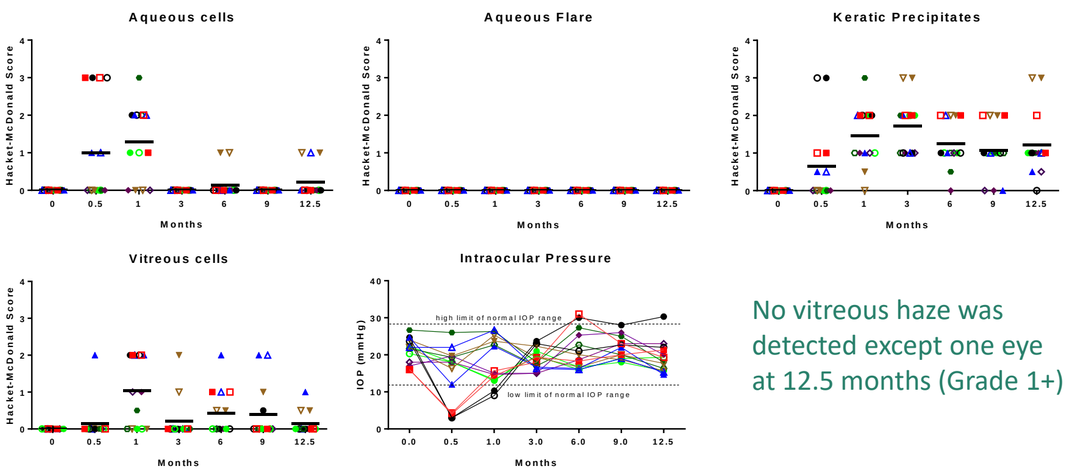


Area of CNV complex evaluated 2 and 4 weeks post-laser photocoagulation.



**** P<0.0001, Mann-Whitney U test. There was no statistical difference between the ADVM-022 and aflibercept groups.

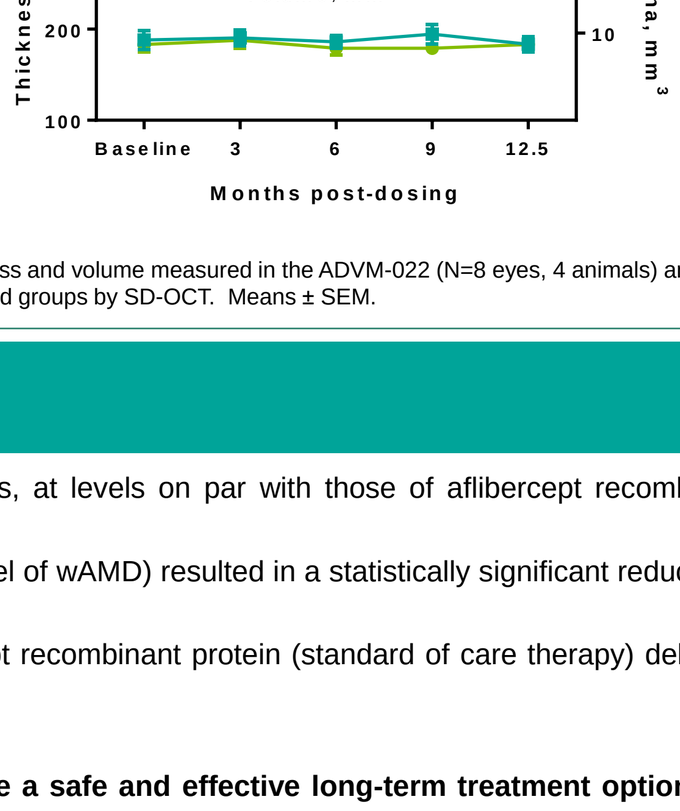
ADVM-022 related adverse events were mild to moderate and largely transient, resolving without anti-inflammatory treatment



No vitreous haze was detected except one eye at 12.5 months (Grade 1+)

Horizontal bars show mean values. The decrease in IOP coincides with a peak in markers of inflammation. Each symbol represents one individual eye. (N=14 eyes, 7 animals).

Prolonged exposure of retina to aflibercept following ADVM-022 administration was well tolerated



Retinal thickness and volume measured in the ADVM-022 (N=8 eyes, 4 animals) and vehicle (N=8 eyes, 4 animals) treated groups by SD-OCT. Means ± SEM.

Conclusions

- A single IVT injection of ADVM-022 provided sustained ocular expression of aflibercept up to 16 months, at levels on par with those of aflibercept recombinant protein within the therapeutic window of the approved standard of care therapy
- A single IVT injection of ADVM-022 administered more than one year prior to laser-induced CNV (NHP model of wAMD) resulted in a statistically significant reduction of clinically relevant Grade IV lesions, as measured by fluorescein angiography and SD-OCT
  - The efficacy of ADVM-022 13 months after its delivery was comparable to the efficacy of aflibercept recombinant protein (standard of care therapy) delivered at the time of the laser
- ADVM-022 was well tolerated, with no serious adverse events
- **A single IVT administration of ADVM-022 delivering a continuous supply of aflibercept may provide a safe and effective long-term treatment option for patients suffering from wAMD**