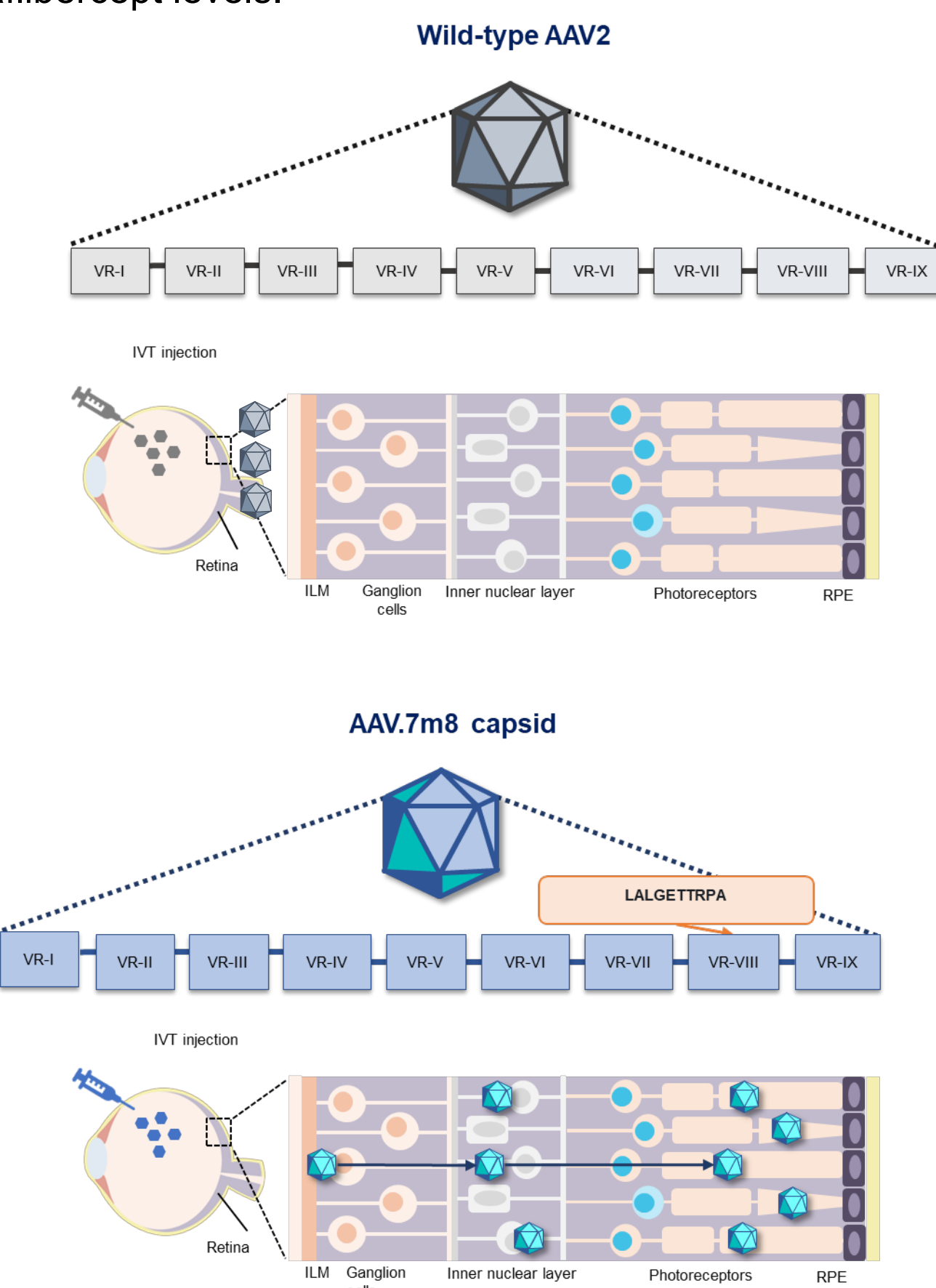


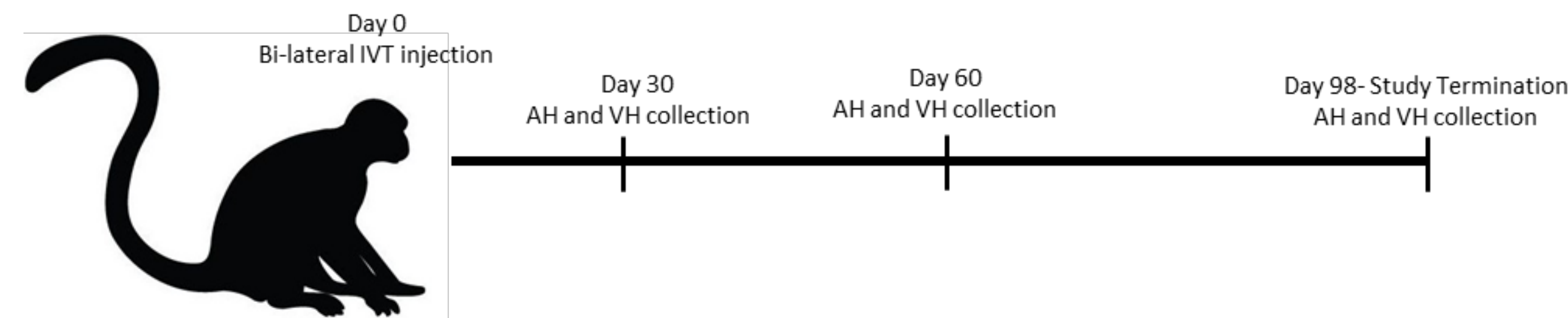
## BACKGROUND

- Intravitreal (IVT) administration of anti-vascular endothelial growth factor (VEGF) (such as aflibercept) is the standard of care for neovascular age-related macular degeneration (nAMD).
- The need for frequent injections can result in fluctuations in central subretinal fluid and impacts best corrected visual acuity.
- ADVM-022 is a gene therapy product of aflibercept packaged in the engineered AAV.7m8 capsid as shown in **Figure 1**.
- A single IVT administration of ADVM-022 resulted in durable aflibercept levels out as long as 104 weeks, as demonstrated in the ongoing, long-term clinical study, OPTIC.
- ADVM-022 has been shown to reduce annual injection frequency by >80%, and in most patients eliminate the need for any additional injections of anti-VEGF at both 2E11 vg/eye and 6E11 vg/eye in human patients (see Oral Presentation by Szilárd Kiss, May 19, 9:30-9:45 AM).
- Previous non-clinical studies demonstrated a nearly flat dose response suggesting a lower dose could also yield efficacious aflibercept levels.



**Figure 1. ADVM-022 is packaged in the engineered AAV.7m8 capsid, a 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.<sup>1</sup> AAV, adeno-associated virus; ILM, inner limiting membrane; IVT, intravitreal; RPE, retinal pigment epithelium; VR, variable region.

## METHODS



\*No steroids or other anti-inflammatory drugs were used at any point before or during the study, to unmask the extent of dose-related inflammatory response.

**Figure 2. Overview of NHP study design and vitreous humor (VH) and aqueous humor (AH) sample collection.**

**Table 1. Summary of Ocular Examinations.**

Ocular Safety Assessments	
•	Ophthalmic exams
•	Tonometry (intraocular pressure)
•	Optical Coherence Tomography (OCT)
•	Electroretinography (ERG)

- Ocular examinations were performed both pretreatment and throughout the study.
- Slit lamp biomicroscopy was used to examine the anterior segment, lens, and anterior vitreous including the iris by transillumination. The anterior segment was scored using the modified Hackett McDonald scale. Indirect ophthalmoscopy was used to examine the vitreous, fundus and optic disc.
- Tonometry was performed at approximately the same time of day throughout the study as when the IVT injections were performed.

**Table 2. Summary of NHP Study Design.**

Group	Test Material	Dose Level (vg/eye)	Human Equivalent Dose, HED (v/g/eye)	Dose Volume (mL/eye)	Number of NHP subjects
1	Vehicle	0	0	0.05	2
2	ADVM-022	3E10	6E10	0.05	4
3	ADVM-022	1E11	2E11	0.05	4

\*NHP subjects underwent bilateral administration of ADVM-022 or vehicle control.

**Table 3. Collection Schedule of Aqueous and Vitreous Humors.**

Group	NHP ID	Day 30 Collection		Day 60 Collection		Day 98 Collection	
		AH	VH	AH	VH	AH	VH
1	1001	OS	OS	OS	OS	OS	OS
	1102	OU	OS	OU	OU	OU	OU
2	2001	OS	OS	OS	OS	OS	OS
	2002	OS	OS	OS	OS	OS	OS
	2103	OU	OS	OU	OU	OU	OU
	2004	OU	OS	OU	OU	OU	OU
3	3001	OS	OS	OS	OS	OS	OS
	3002	OS	OS	OS	OS	OS	OS
	3003*	OU	OS	OU	OU	OU	OU
	3004*	OU	OS	OU	OU	OU	OU

\*A subset of vitreous samples were not collected at Day 30 but were collected at later timepoints. This was due to initial uncertainty of the difficulty of sample collection. As a result, the peak levels recorded for vitreous may be artificially low due to fewer timepoints collected for a subset of samples. Furthermore, we anticipate the lower values recorded at later timepoints to be the result of anti-drug antibodies (ADA).

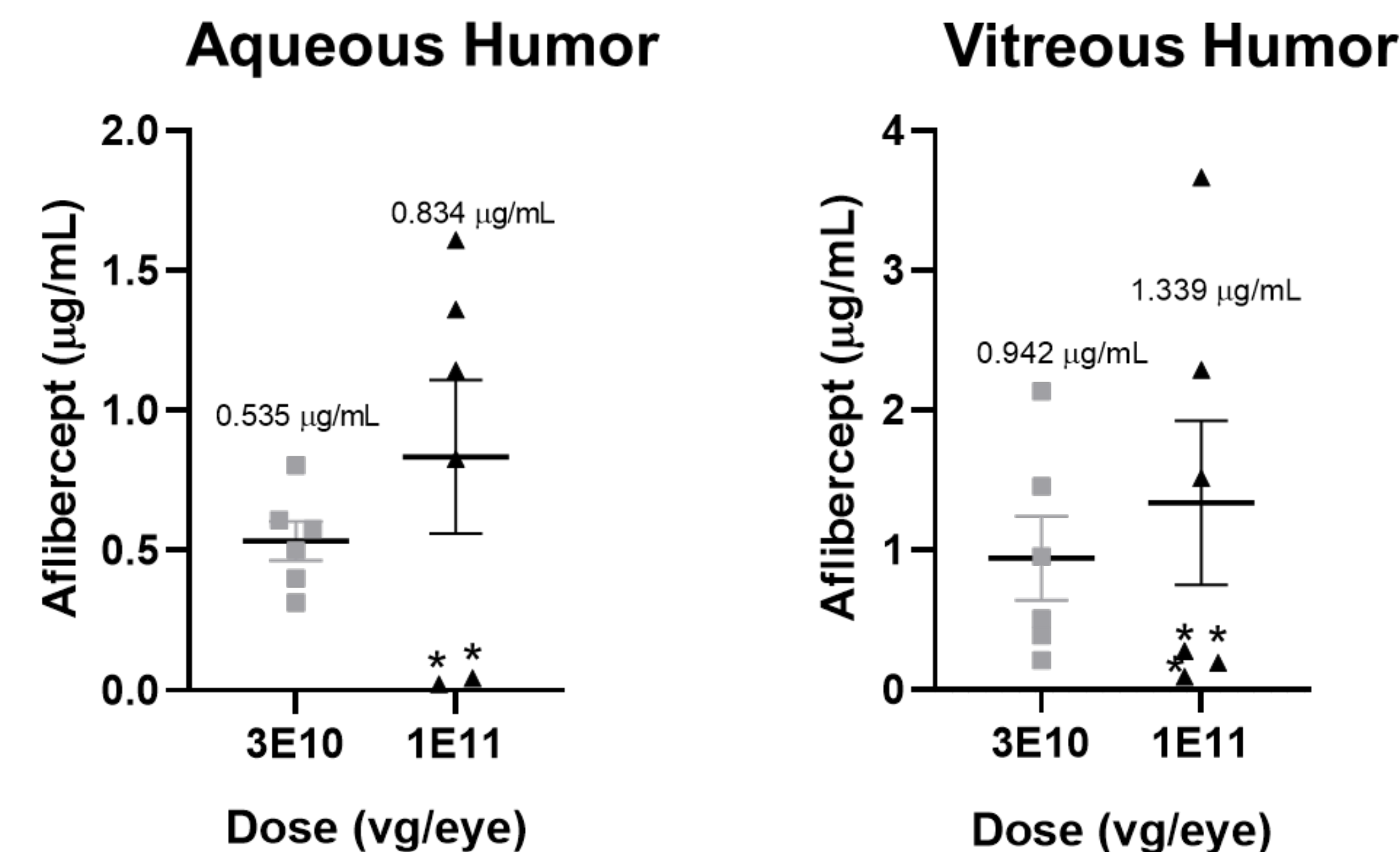
## RESULTS

### Summary of ADVM-022 Tolerability

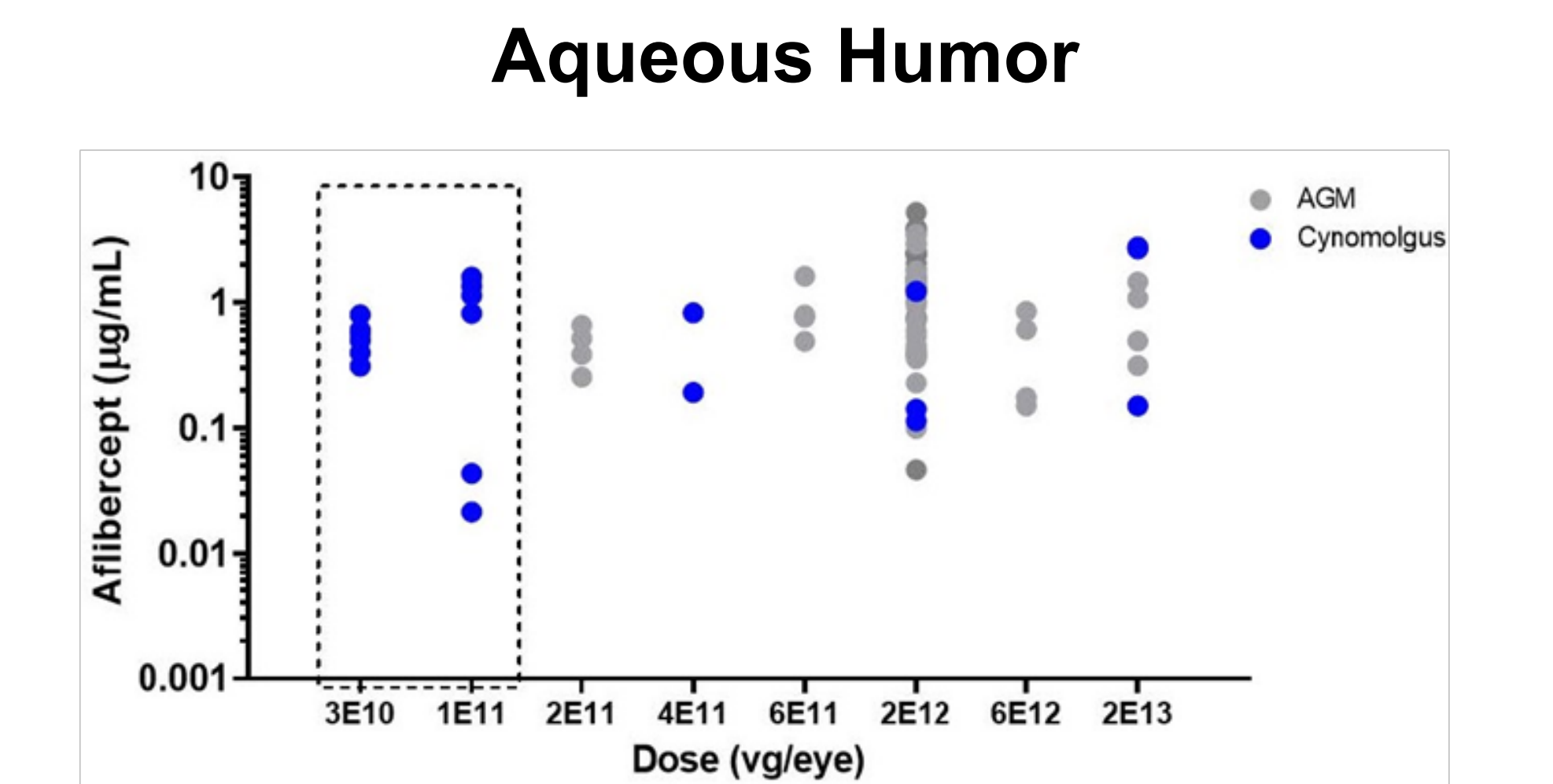
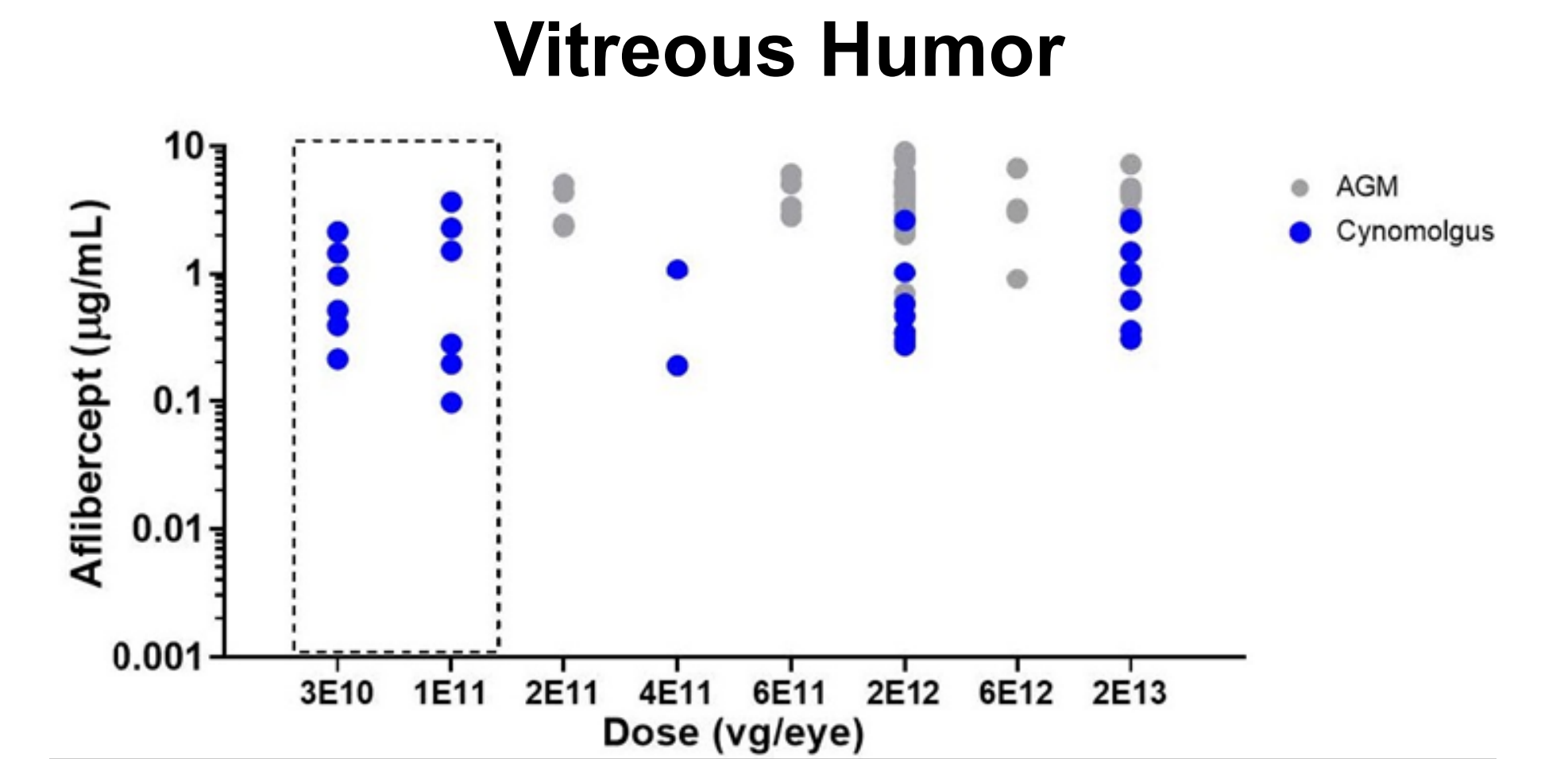
- Tested doses of ADVM-022 in NHP subjects were well tolerated.
- No adverse systemic clinical signs were observed.
- In life observations were dose-dependent and limited to non-adverse slight to mild dose-dependent ocular inflammation characterized by pigment and cells in the VH.
- Microscopic findings were limited to minimal mononuclear cell infiltrations, considered non-adverse based on minor severity as shown in **Figure 3**.
- NOEAL has been determined at 1E11 vg/eye (HED 2E11 vg/eye).

Treatment	NHP ID	0	3	8	15	21	25	36	50	64	78	92	Color Codes
Vehicle	1001 OD	0	0	0	0	0	0	0	0	0	0	0	4
	1001 OS	0	0	0	0	0	0	0	0	0	0	0	3
	1002 OD	0	0	0	0	0	0	0	0	0	0	0	2
	1002 OS	0	0	0	0	0	0	0	0	0	0	0	1
3E+10	2001 OD	0	0	0	0	0	0	0	0	0	0	0	0.5
	2001 OS	0	0	0	0	0	0	1	1	0.5	0	0	0
	2002 OD	0	0	0	0	0	0	0	0	0	0	0	0
	2002 OS	0	0	0	0	0	0	0	0	0	0	0	0
	2103 OD	0	0	0	0	0	0	0	0	0	0	0	0
	2103 OS	0	0	0	0	0	0	0	0	0	0	0	0
	2004 OD	0	0	0	0	0	0	0	0	0	0	0	0
	2004 OS	0	0	0	0	0	0	0	0	0	0	0	0
1E+11	3001 OD	0	0	0	0	0	0	0	0	0	0	0	0
	3001 OS	0	0	0	0	0	0	0	0	0	0.5	0.5	0
	3002 OD	0	0	0	0	0	0	0	0	0	0	0	0
	3002 OS	0	0	0	0	0	0	0	0	0	0	0	0
	3003 OD	0	0	0	0	0	2	2	2	0.5	0.5	0	0
	3003 OS	0	0	0	0	0	2	2	2	0.5	0.5	0	0
	3004 OD	0	0	0	0	0	2	2	2	2	1	1	1
	3004 OS	0	0	0	0	0	1	2	2	2	1	1	1

**Figure 3. Heat map of ocular scores.** Ocular scores are measured over 92 days.



**Figure 4. Peak aqueous aflibercept values exceeded or approached 0.5 µg/mL after a dose of 3E10 vg/eye.** NHP subjects were treated with a dose of 3E10 (gray) or 1E11 (black) vg/eye. The peak aflibercept value detected in aqueous and vitreous humors for each NHP subject is represented here. Black horizontal bars denote group mean, black vertical bars denote SEM, and asterisks (\*) denote outlier samples which are hypothesized to be the result of anti-drug antibodies (NHP IDs 3003 and 3004).



**Figure 5. Historical data shows a near flat dose response over 3 logs.** Historical NHP studies in support of ADVM-022 included African green monkeys (AGM, grey) or cynomolgus (blue). NHPs were administered ADVM-022 at doses spanning nearly 3 logs (3E10 – 2E13 vg/eye). Peak aflibercept levels for each NHP subject in each study were measured via aflibercept ELISA and recorded. The samples from the current study are outlined with dotted boxes.

## CONCLUSIONS

- IVT administration of ADVM-022 was well tolerated by NHP subjects including no observed adverse systemic clinical signs.
- NOEAL found in this study: 1E11 vg/eye.
- The findings from the non-clinical NHP study suggest administration of ADVM-022 at doses as low as 3E10 vg/eye (human equivalent dose of 6E10 vg/eye) are anticipated to provide therapeutic levels of aflibercept in the clinic.
- These data are informative for the dosing regime in the planned Phase II study.

### References:

1. Grishanin, R et al. *Mol Ther.* 2019;27:118–129

**Disclosures:** The authors are employees at Adverum Biotechnologies, Inc., and hold shares at the company.

**Acknowledgements:** Charles River Laboratory ran the NHP study and performed ophthalmic evaluations.