A GLP-Compliant Toxicology and Biodistribution Study of ADVM-062 (AAV.7m8-L-opsin), a Novel Gene Therapy Product Being Developed as a Potential Single Intravitreal Administration for the Treatment of Blue Cone Monochromacy

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Disclosure

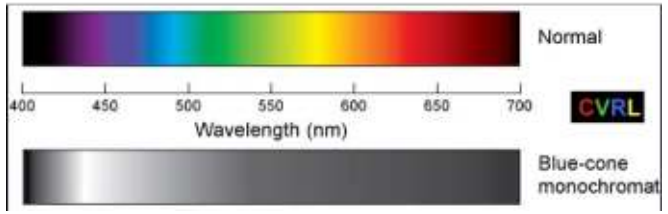
- I am an employee of Adverum Biotechnologies and hold shares in the company.

Disease Overview – Blue Cone Monochromacy

Blue Cone Monochromacy (BCM) is a X-linked recessive hereditary condition caused by the absence of function in the L and the M opsin genes and can manifest in:

- Decreased visual acuity
- Severe loss of color discrimination
- Light aversion
- Nystagmus

- Vision is derived only from the remaining 5% of preserved blue cones and unaffected rod photoreceptors
- Individuals with BCM have visual impairments to important aspects of daily living (facial recognition, learning, reading, daylight vision)
- Orphan disease with a prevalence of less than 1 to 9 in 100,000 males, worldwide
- No available treatments/announced programs in clinical development



Gene therapy, aimed to restore opsin expression in foveal cones, is considered a potential treatment. However, subfoveal injection of vector poses a risk to the fragile central retinal structure in BCM patients.

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Product Vision: ADVM-062 - A One-Time Intravitreal Gene Therapy Vector to Restore Functional L-Opsin Expression in Cones of BCM Patients

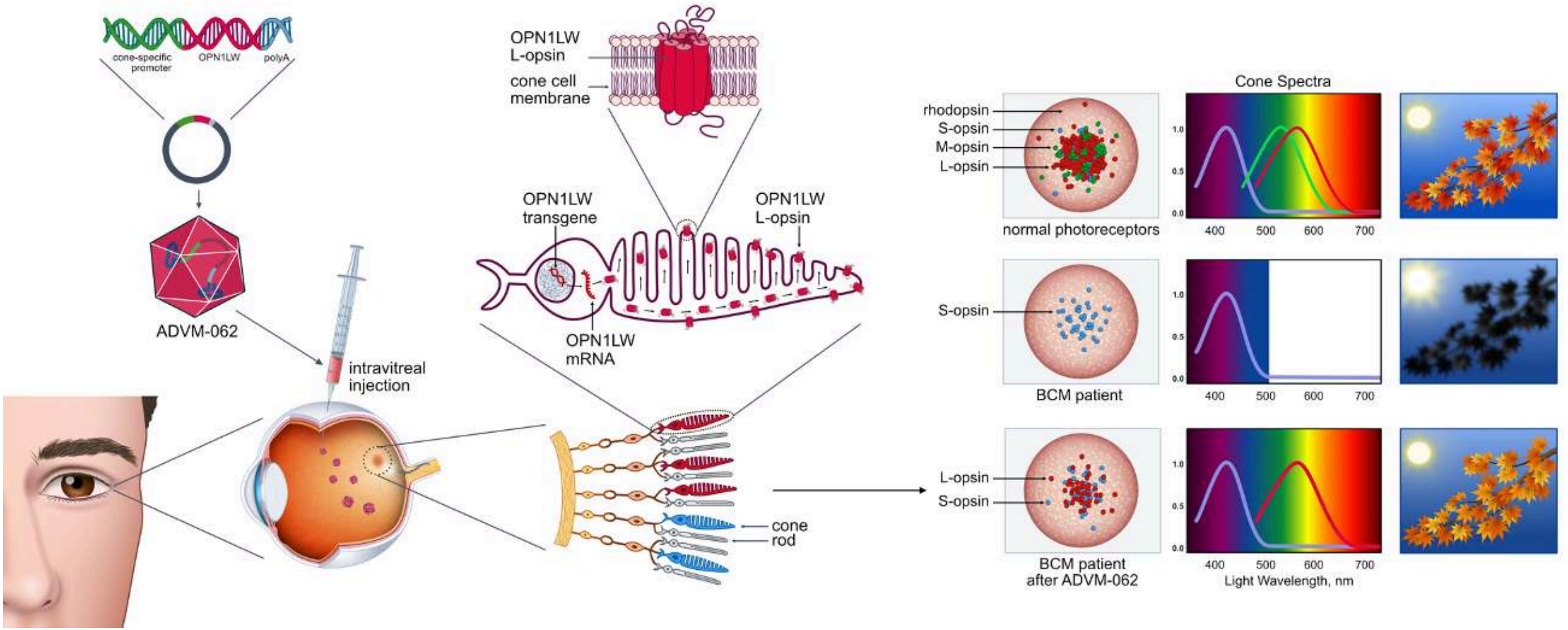

Illustration: Gardenia Gonzalez Gil

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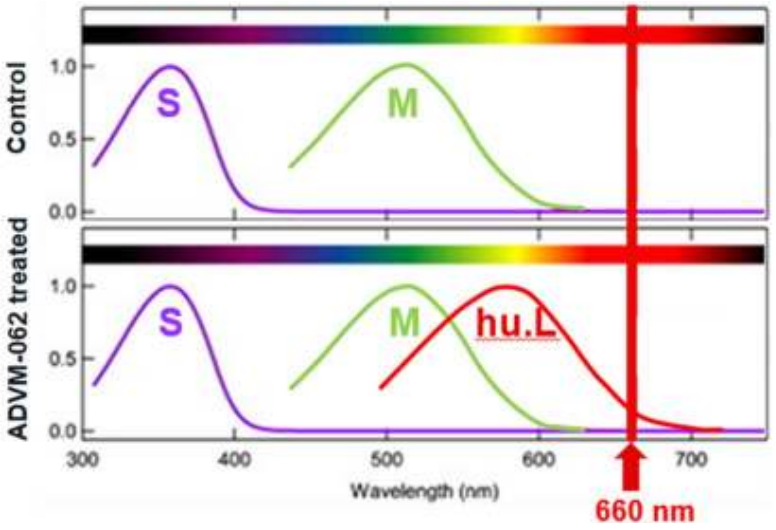
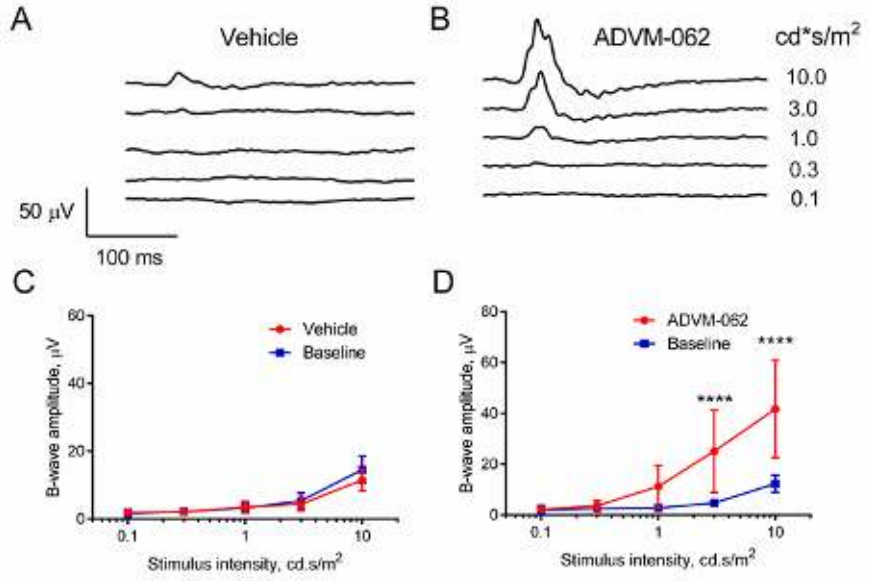
Proof of Functional Activity of ADVM-062 in Rodents

Single IVT administration of ADVM-062 effectively transduces gerbil cone photoreceptors and produces *de novo* response to long wavelength light

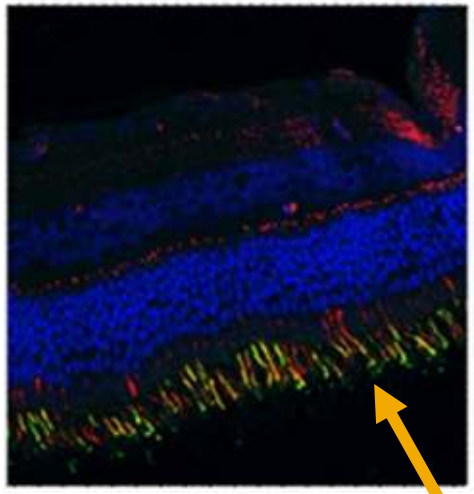
ADVM-062 is expected to expand retinal sensitivity of dichromatic gerbil to red light



ERG responses to red light stimulus (660 nm) at increasing light intensities



Localization of human L-opsin in gerbil cones detected using ADVM-062.myc



Ganglion cell layer

Inner nuclear layer

Outer nuclear layer

L-opsin.myc
Cone arrestin
DAPI (nuclei)

Cone photoreceptor outer segments

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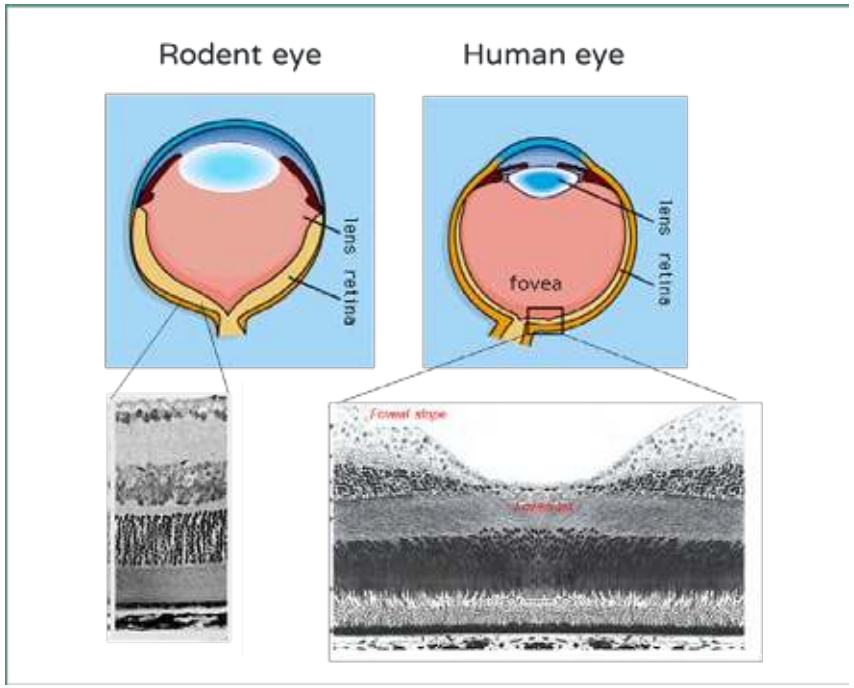
Challenges in BCM Treatment Discovery and Development

- Differences in the ocular anatomy and physiology of rodent and human eyes
  - Presence of fovea in primates but not in rodents
  - Different thickness profile of ILM (inner limiting membrane) – a major barrier for retinal gene therapy



- Close identity of human L-opsin and macaque L-opsin poses a challenge in NHP studies
- Gene therapy aimed to restore opsin expression in foveal cones is considered a potential treatment

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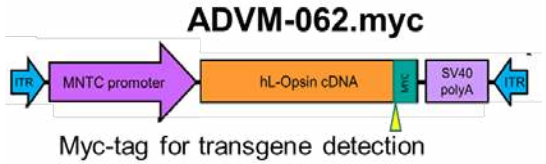
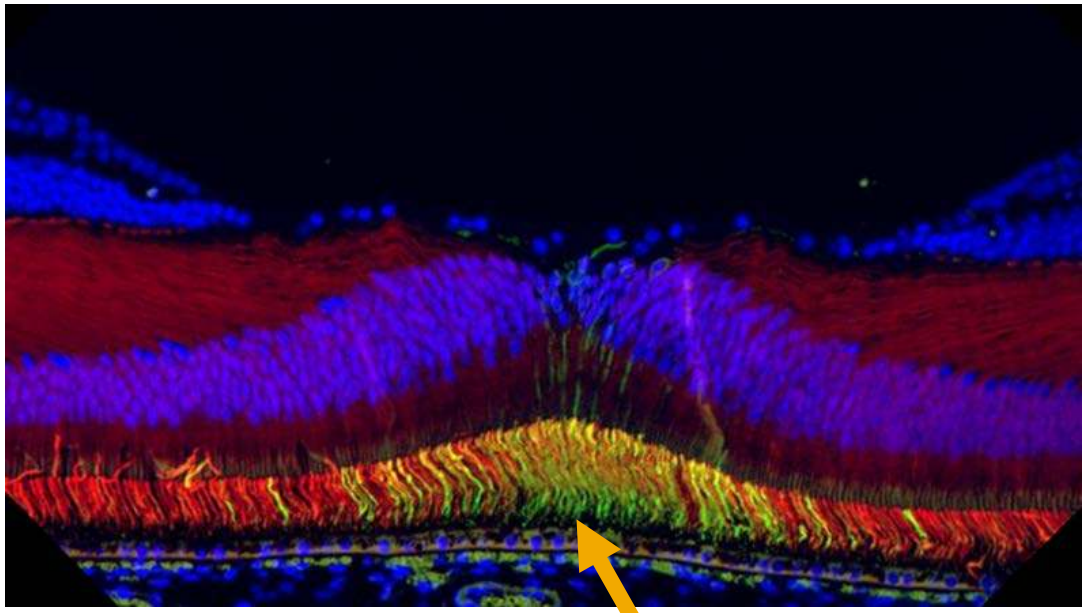
Evaluation of Dose-dependent Activity of ADVM-062 in NHPs by Enumeration of Transduced Foveal Cones in NHPs Using ADVM-062.myc



Section of ADVM-062.myc Dosed NHP eye - central retina through fovea

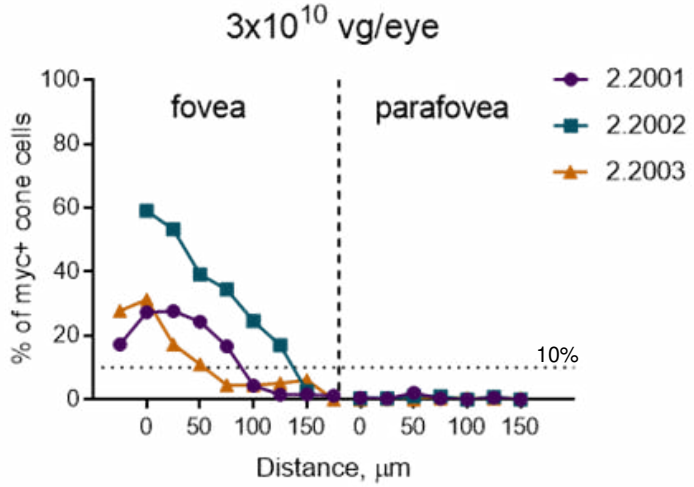


Dose: 3x10^{10} vg/eye

Cone photoreceptor outer segments

Green: human L-opsin.myc
Red: cone arrestin
Blue: DAPI, *nuclei*

Serial Sections of the Fovea and Parafovea for L-Opsin.myc-positive cone enumeration



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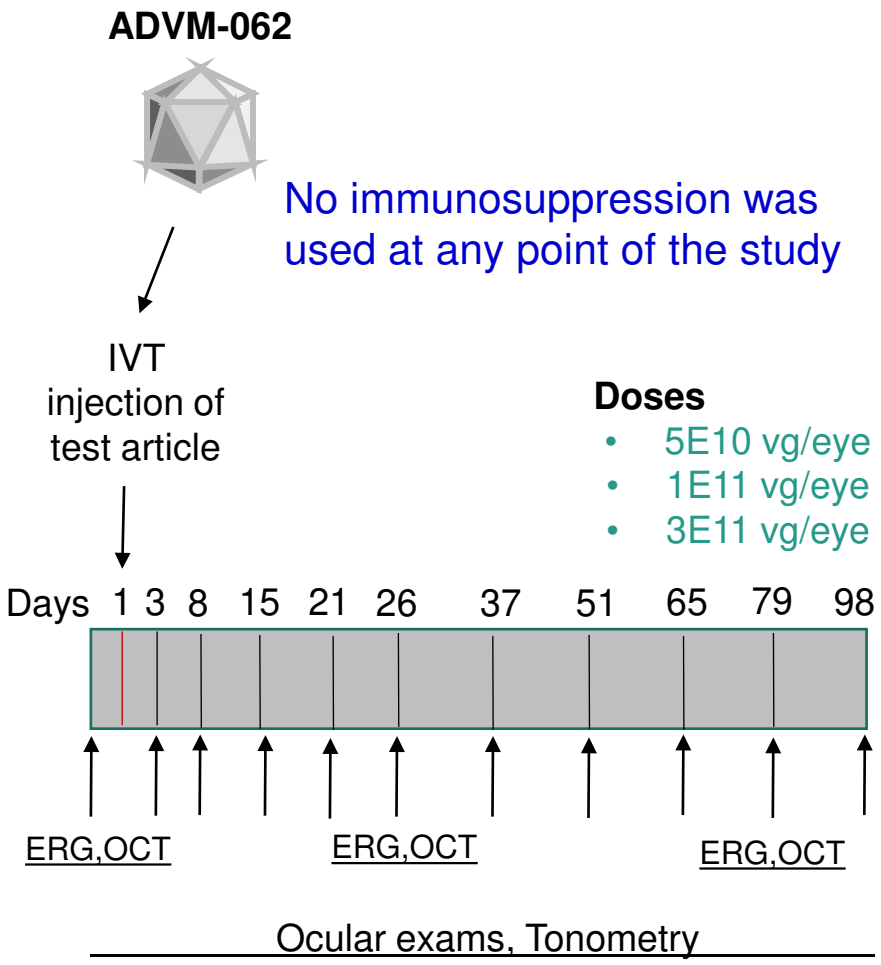
Non-Human Primate Data from GLP Toxicology Study of ADVM-062 Study Overview



Ocular Safety Assessments

- Ophthalmic exams
- Tonometry (intraocular pressure)
- Optical Coherence Tomography (OCT)
- Electroretinography (ERG)

Overview of Findings

- ADVM-062 was well tolerated at the doses up to 3E11 vg/eye
  - Dose of 5E10 vg/eye resulted in no ophthalmic, macroscopic, or microscopic findings.
  - Doses of 1E11 vg/eye and 3E11 vg/eye resulted in slight to mild inflammation characterized by pigment and cells in the vitreous.
- No IOP changes
- One test-article unrelated mortality due to the anesthesia
- Microscopic finding – minimal mononuclear infiltrates in one eye at 3E11 vg/eye
- **No observed adverse effect level (NOAEL) identified as 3E11 vg/eye**

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ADVM-062 Doses Were Well-Tolerated in GLP Tox NHP Study

No anti-inflammatory steroids were used at any timepoint of the study.

Vitreous Cells Inflammation Scores*

Dose	Days	0	3	8	15	21	26	37	51	65	79	93	Color Codes
Vehicle	1001 OD	0	0	1	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
5.00E+10	2001 OD	0	0	0	0	0							0.5
	2001 OS	0	0	0	0	0							0
	2002 OD	0	0	0	0	0	0	0	0	0	0	0	
	2002 OS	0	0	0	0	0	0	0	0	0	0	0	
	2003 OD	0	0	0	0	0	0	0	0	0	0	0	
	2003 OS	0	0	0	0	0	0	0	0	0	0	0	
1.00E+11	3001 OD	0	0	0	0	0	0	0	0	0	0	0	
	3001 OS	0	0	0	0	0	0	0.5	0	0	0	0	
	3002 OD	0	0	0	0	0	2	0	0	0	0	0	
	3002 OS	0	0	0	0	0	2	1	0	0	0	0	
	3003 OD	0	0	0	0	0	0	0	0	0	0	0	
	3003 OS	0	0	0	0	0	0	0	0	0	0	0	
3.00E+11	4001 OD	0	0	0	0	0	0	1	0	0.5	0.5	0.5	
	4001 OS	0	0	0	0	0	0	1	0.5	0	0	0	
	4002 OD	0	0	0	0	0	0	1	0.5	0	0	0	
	4002 OS	0	0	0	0	0	0	1	0.5	0	0	0	
	4003 OD	0	0	0	0	0	0	1	1	0.5	0.5	0.5	
	4003 OS	0	0	0	0	0	0	0	0.5	0.5	0.5	0.5	

*Aqueous cells, Aqueous flare and Vitreous haze scores were zero. No KPs found.

Intraocular Pressure, IOP (mmHg)

Dose	Days	0	3	8	15	21	26	37	51	65	79	93	Color Codes
Vehicle	1001 OD	16	17	17	16	17	16	17	18	19	20	18	≤5 mm.Hg
	1001 OS	16	15	17	16	17	16	18	19	18	19	17	6 - 11 mm.Hg
	1002 OD	19	18	19	19	22	20	20	21	19	20	19	≥12 mm.Hg
	1002 OS	19	19	20	21	22	20	20	21	20	20	20	
5.00E+10	2001 OD	18	13	19	15	18							
	2001 OS	18	14	16	15	18							
	2002 OD	17	15	17	15	16	16	17	17	18	18	17	
	2002 OS	17	17	18	16	17	18	18	18	18	18	18	
	2003 OD	14	13	14	15	15	16	15	16	14	15	14	
	2003 OS	15	15	15	15	13	15	15	16	14	17	14	
1E+11	3001 OD	18	17	20	19	20	20	20	21	23	22	21	
	3001 OS	18	17	18	18	20	19	21	19	23	22	20	
	3002 OD	18	15	17	17	19	17	18	19	20	19	18	
	3002 OS	18	17	16	17	20	17	18	19	19	17	17	
	3003 OD	15	14	18	16	18	17	20	19	20	20	18	
	3003 OS	16	18	19	17	19	18	20	21	19	20	20	
3.00E+11	4001 OD	20	20	16	21	20	20	19	20	21	20	22	
	4001 OS	21	20	16	20	19	21	19	21	21	18	22	
	4002 OD	18	16	18	15	17	14	22	20	19	17	19	
	4002 OS	17	16	17	21	16	14	18	20	19	18	19	
	4003 OD	18	14	17	20	17	15	16	17	18	20	20	
	4003 OS	16	14	17	19	17	16	15	19	17	18	18	

IOPs were within normal range at all doses.

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Summary of GLP Tox Study

- ADVM-062 was well tolerated at all doses tested
- Self-resolving dose-dependent inflammation (trace to mild grade) observed at the mid and high dose
- No local or systemic anti-inflammatory treatments were used at any point of the study
- No major test article-related adverse events were observed for the duration of the study
- No transillumination defects observed
- IOP for all dose groups were within the normal ranges through the course of the study
- No observed adverse effect level (NOAEL) for the study was 3E11 vg/eye (high dose)
- Nonclinical data provide strong POC of ADVM-062 and demonstrate tolerability of ADVM-062 to support a submission of an investigational new drug (IND) application
- **FDA has recognized the patient need by granting Orphan Drug Designation to ADVM-062**

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