



Gaining Momentum in Gene Therapy

Corporate Presentation

December 2017

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Adverum is a Clinical-Stage Gene Therapy Company with Industry-leading Capabilities



Industry-leading AAV platform and capabilities:

- Proprietary vector development to engineer next-generation vectors
- In-house manufacturing - Process development, assay development



Robust pipeline:

- ADVM-043 for A1AT deficiency – Began enrollment in ADVANCE Phase 1/2 Trial 4Q17
- ADVM-053 for HAE – Plan to file IND in 2H18
- ADVM-022 for wet AMD – Plan to file IND in 2H18



\$187M in cash* to fund lead programs through the end of 2019



Leadership team with **extensive clinical development expertise**

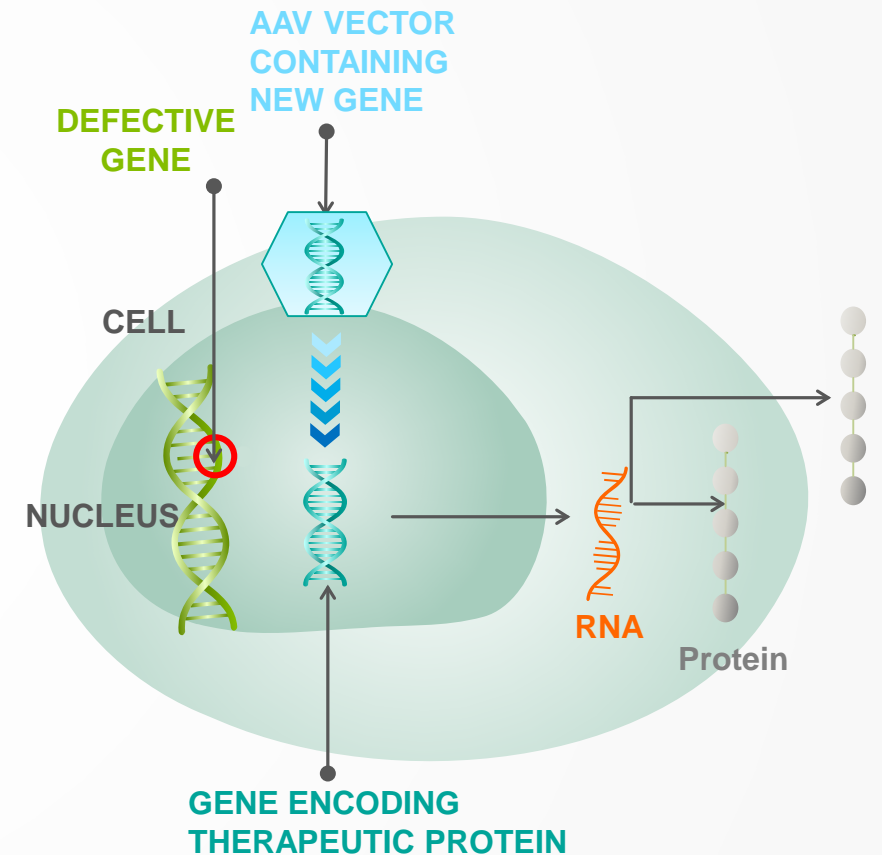
Adverum's Approach: AAV Gene Therapy Platform

Efficacy



- › Highly efficient transfer of DNA to patient
- › Long-lasting potential

Safety

- › Non-integrating vector genome
- › Therapeutic proteins expressed from within, rather than introducing an exogenous protein
- › No known associations with disease
- › Safely used in more than 100 gene therapy clinical trials to date¹



Advancing Gene Therapies for Serious Rare & Ocular Diseases

Product Candidate	Stage of Development		
	Research	Preclinical	Phase 1/2
Lead Programs – Worldwide Rights			
ADVM-043 (Rare Disease)	ADVANCE Trial for Alpha-1 Antitrypsin (A1AT) Deficiency		
ADVM-053 (Rare Disease)	Hereditary Angioedema (HAE)		
ADVM-022 (Ocular Disease)	Wet Age-related Macular Degeneration (wAMD)		
Partnered Programs			
Up to 5 Undisclosed Targets	Inherited Retinal Disease		 Collaboration
X-linked Retinoschisis and 3 Undisclosed Targets	Ophthalmic Disease		 Collaboration

Adverum's Lead Gene Therapy Programs



**Alpha-1 Antitrypsin
(A1AT) Deficiency**

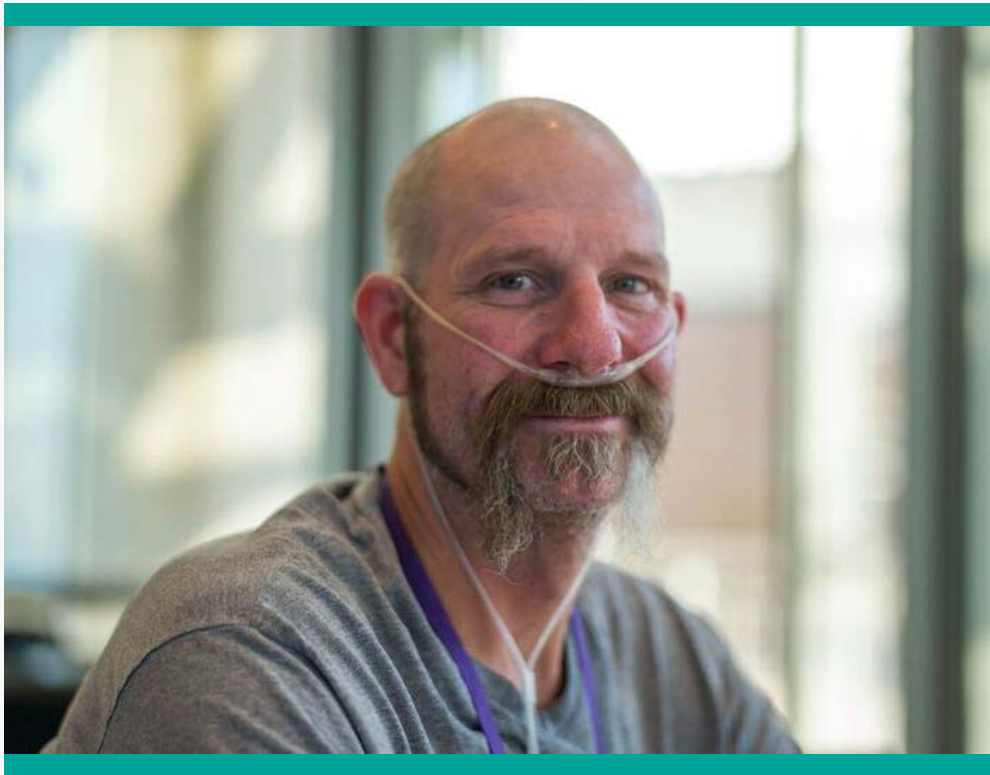


**Hereditary Angioedema
(HAE)**



**Wet Age-related
Macular Degeneration
(wAMD)**

A1AT Deficiency is an Orphan Disease Which Can Lead to Worsening Lung Function



- › 100,000 U.S. patients¹
- › Genetic mutation results in very low levels of A1AT
 - A1AT deficiency is associated with premature emphysema
- › Challenging compliance
 - Need for weekly IV infusions² (\$100K annually)
 - Worsening lung function from underdosing

¹ Healthcare Provider's Guide. The Alpha-1 Foundation. Version 2.0 (2015).

² Glassia, Prolastin-C, Aralast NP, Zemaira.

Potential to Treat A1AT Deficiency With ADVM-043

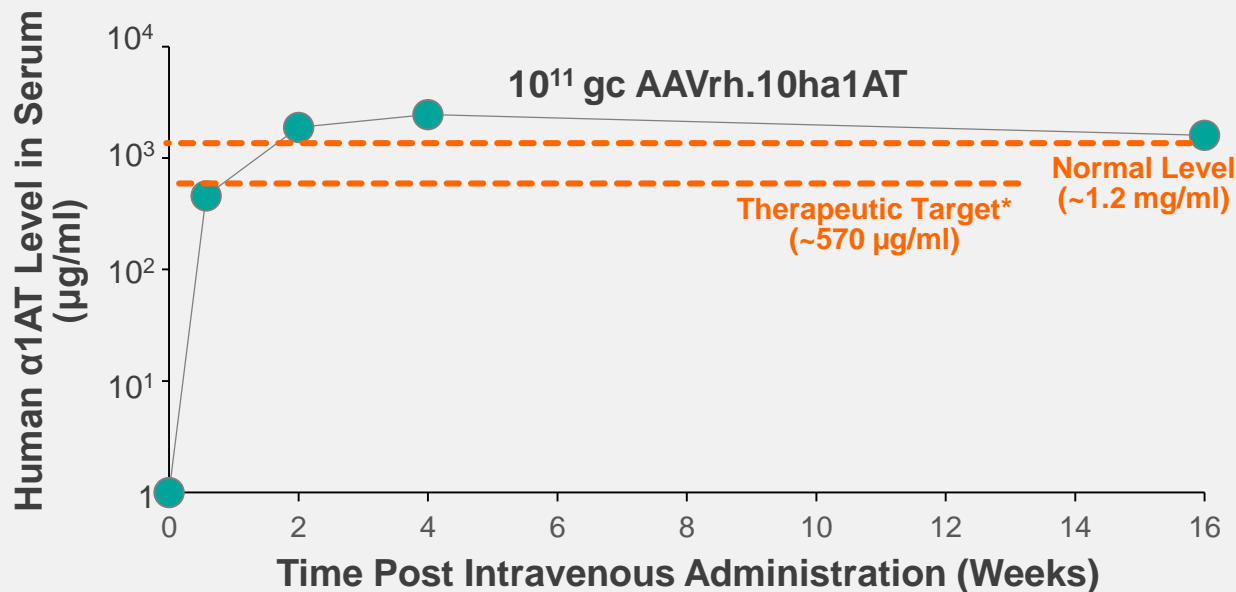


- › **Single administration of ADVM-043** demonstrated robust A1AT expression in preclinical proof-of-concept study
 - A1AT expression above therapeutic levels in mice following intravenous or intrapleural administration
- › Evidence of stable long-term expression of hA1AT mRNA out to 1 year following intrapleural administration in non-human primates¹
- › ADVM-043 (AAVrh.10-A1AT) has the potential to induce stable, long-term A1AT expression at therapeutic levels
- › Began enrolling patients in the ADVANCE Phase 1/2 trial in December 2017

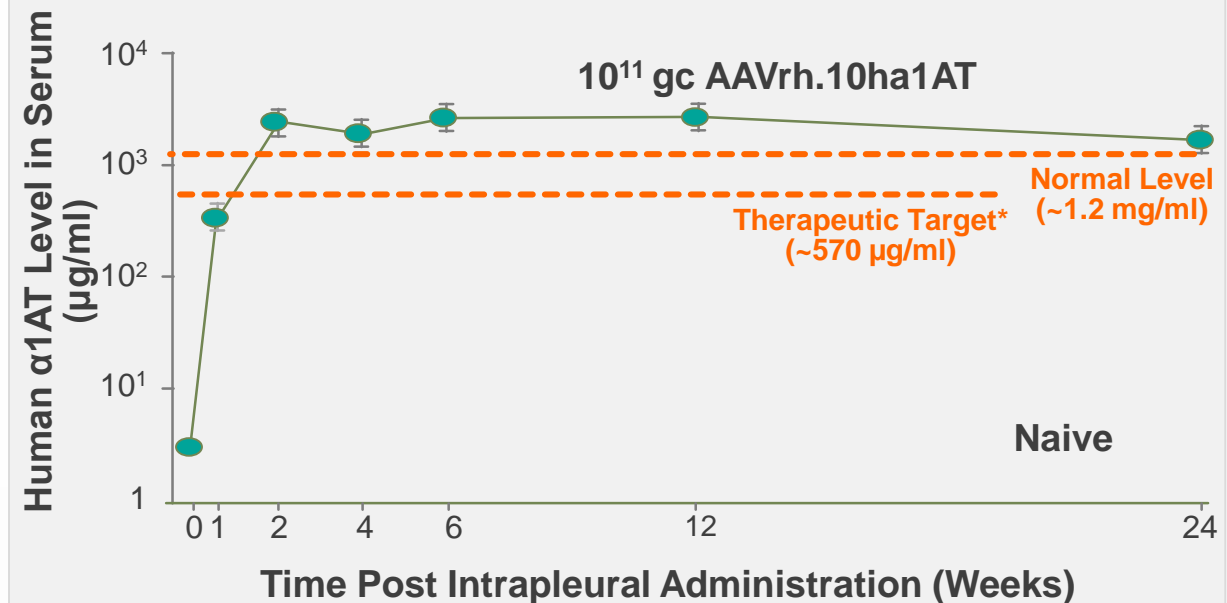
Proof-of-concept Study: Single Administration of ADVM-043 Induces Stable, Long-term Expression of hA1AT

Human A1AT Expression in Serum after ADVM-043 Administration in Mice

Intravenous (IV) Delivery¹



Intraleural (IP) Delivery²



*Note: Therapeutic Target is based on serum levels demonstrated by approved standard-of-care therapies

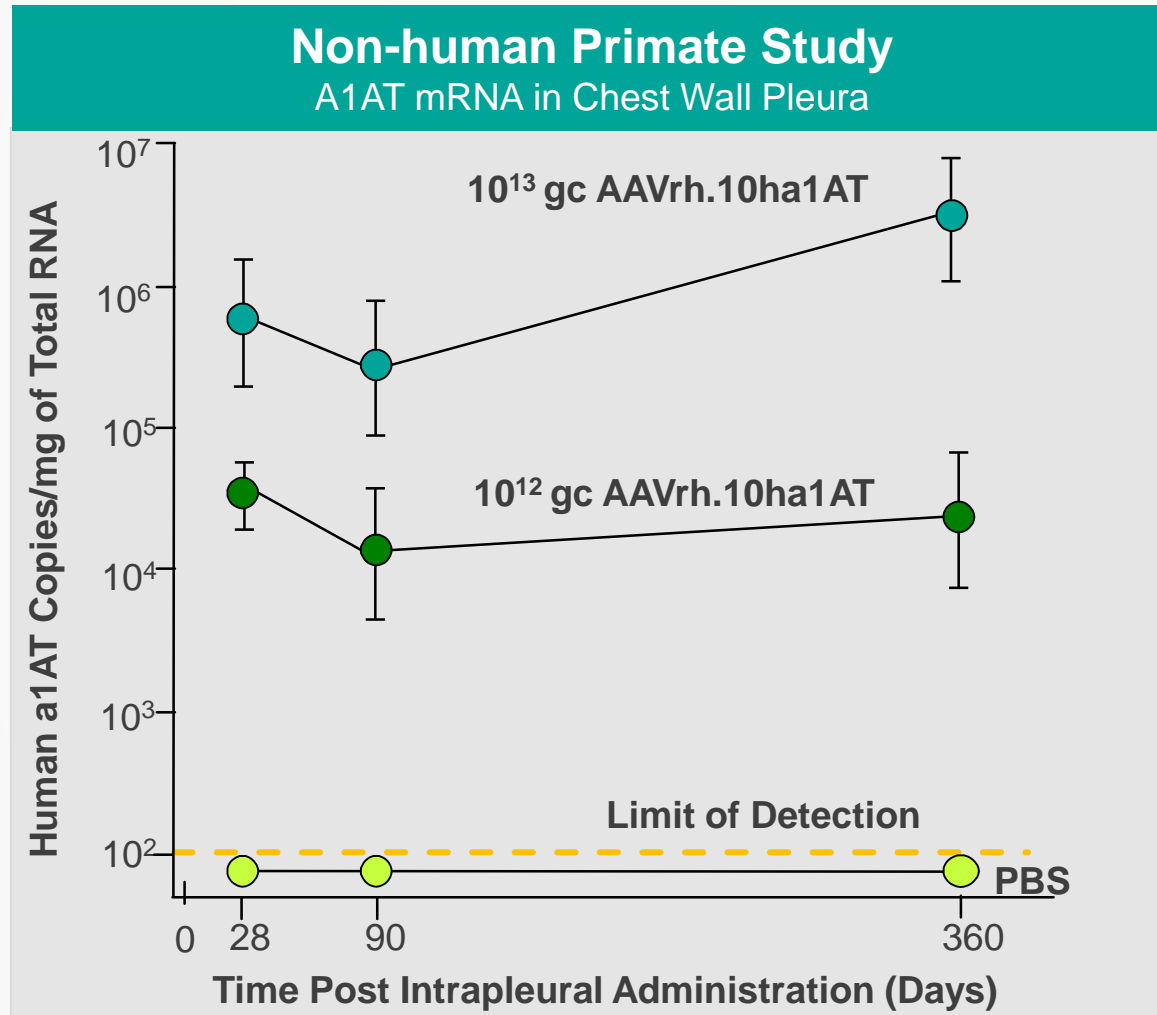
Note: 1.2 mg/ml is approximately equivalent to 20µM; 570 µg/ml is approximately equivalent to 11µM

1 Company data on file

2 High Levels of Persistent Expression of A1-Antitrypsin Mediated by the Nonhuman Primate Serotype rh.10 Adeno-associated Virus Despite Preexisting Immunity to Common Human

Adeno-associated Viruses, Mol Ther Vol. 13, No. 1 (January 2006), De et al.

Proof-of-concept: Single Administration of ADVM-043 Induces High, Stable Human A1AT mRNA Expression Out to 1 Year



Intrapleural (IP) Delivery¹

- Stable expression of human A1AT mRNA >1 year after single administration

ADVANCE Phase 1/2 Trial: Preliminary Data Expected in 2H18

ADVANCE Phase 1/2 Clinical Trial ADVM-043 for A1AT Deficiency

Key Entry Criteria	Multi-center, Open-label Dose Escalation Study (n = Up to 20 Patients)	Endpoints
<ul style="list-style-type: none"> › ≥18 years of age › A1AT genotype ZZ or Z Null › FEV1 >35% predicted › No evidence of liver disease › Neutralizing antibody titer less than 1:5 	<p>Cohort 1 – IV Low Dose (8E13 total vg¹) (n = 2 to 5 Patients)</p> <p>Cohort 2 – IV Intermediate Dose (n = 2 to 5 Patients)</p> <p>Cohort 3 – IV High Dose (n = 2 to 5 Patients)</p> <p>Cohort 4 – IP Dose² (n = 2 to 5 Patients)</p>	<ul style="list-style-type: none"> › Safety and tolerability › Total and M-specific plasma concentrations of A1AT up to 52 weeks

¹ Low dose of 8E13 total vg equivalent to approximately 1E12 vg/kg based on an 80-kg patient

² Cohort 4 may open to evaluate IP administration of ADVM-043 at the dose that provided the best protein expression with IV administration

Adverum's Lead Gene Therapy Programs



**Alpha-1 Antitrypsin
(A1AT) Deficiency**



**Hereditary
Angioedema (HAE)**



**Wet Age-related
Macular Degeneration
(wAMD)**

HAE is an Orphan Disease That is Challenging to Manage



- › 8,000 U.S. patients¹
- › Genetic mutation results in low levels of C1-esterase inhibitor (C1EI)
 - Low C1EI levels lead to sudden swelling/edema of respiratory airways, GI tract, and extremities
- › Challenging management strategy
 - Prophylaxis requires 2-3x/week IV infusions or SC of C1EI²
 - Breakthrough attacks still occur

¹ Decision Resources Group; November 2015. Wu, Jing; Anderson, Sarah.

² Prophylactic use: Cinryze, Haegarda / Acute treatment: Firazyr, Berinet, Ruconest, Kalbitor.

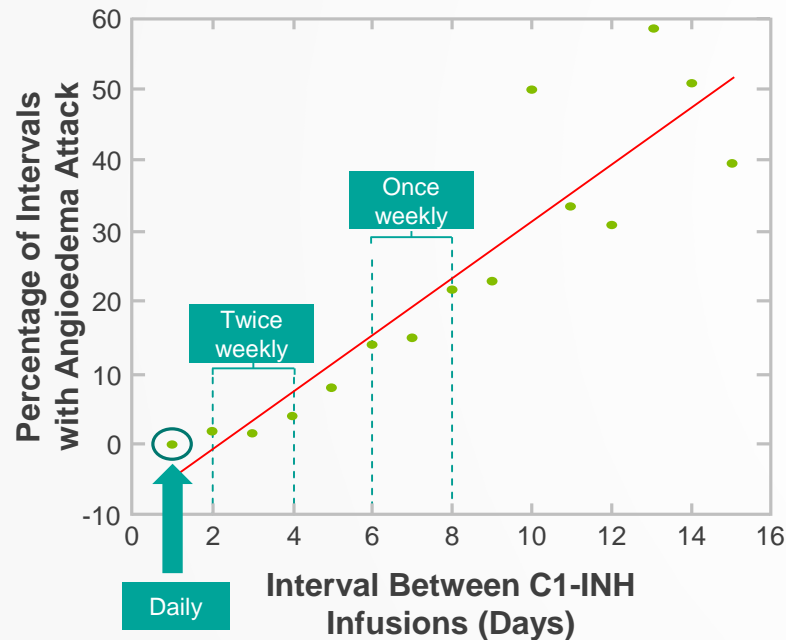
Potential to Prevent HAE Attacks with ADVIM-053



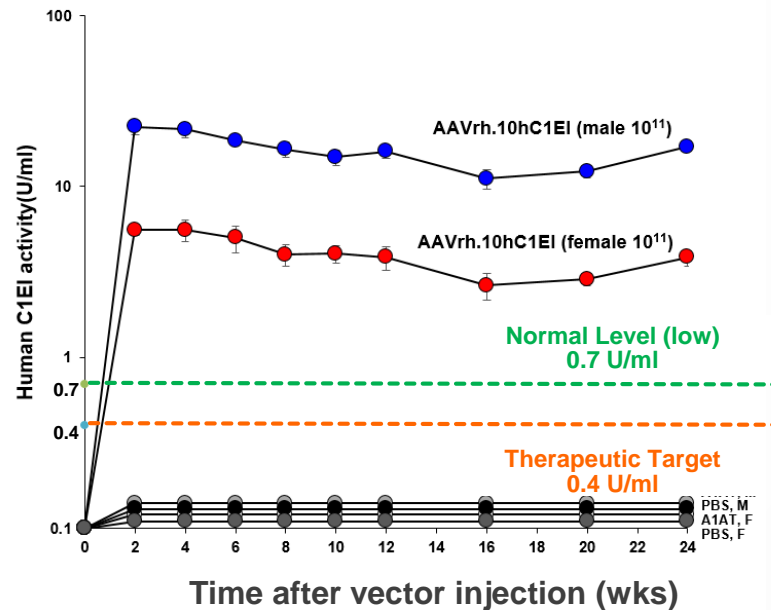
- › **Single intravenous administration of ADVIM-053** showed robust C1EI expression in preclinical studies
 - C1EI protein expression above therapeutic levels
 - Decreased vascular permeability
- › ADVIM-053 (AAVrh.10-C1EI) has the potential to prevent HAE attacks

Proof-of-concept Study: Single IV Administration of ADVM-053 Induces Protein Expression Above Therapeutic Level

Attack rate drops to near zero with daily C1-INH infusion¹ (not clinically practical)



ADVM-053 induces expression above therapeutic level in mice



ADVM-053 showed decrease in vascular permeability to wild type levels

Efficacy in C1EI Deficient Mouse Model



Wild Type²

S63
C1EI Deficient

S63
ADVM-053

24 Weeks Post Injection

Presence of pathology will result in dye leaking into tissues (vasodilation)

¹ Safety and Efficacy of Prophylactic nanofiltered C1-inhibitor in Hereditary Angioedema, Amer J Med 2012;125, 938.e1-938.e7, Zuraw BL and Kalfus I

² Wild type picture is two weeks post injection

Advancing ADVIM-053 for HAE



Next steps

- › Held pre-IND meeting with FDA in 1Q17
- › Performing IND enabling studies and working with a contract manufacturing organization to prepare clinical material
- › Planning to file IND in 2H18

Adverum's Lead Gene Therapy Programs



**Alpha-1 Antitrypsin
(A1AT) Deficiency**



**Hereditary
Angioedema (HAE)**



**Wet Age-related
Macular Degeneration
(wAMD)**

wAMD is a Large Market with Challenging Compliance Issues



Intermediate AMD - 20/20-20/30 Vision

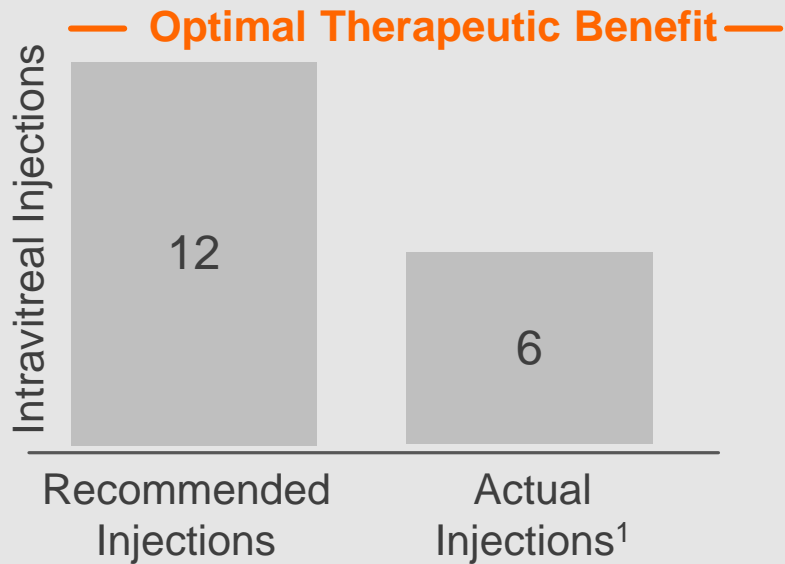


Wet AMD at Diagnosis - 20/80 Vision

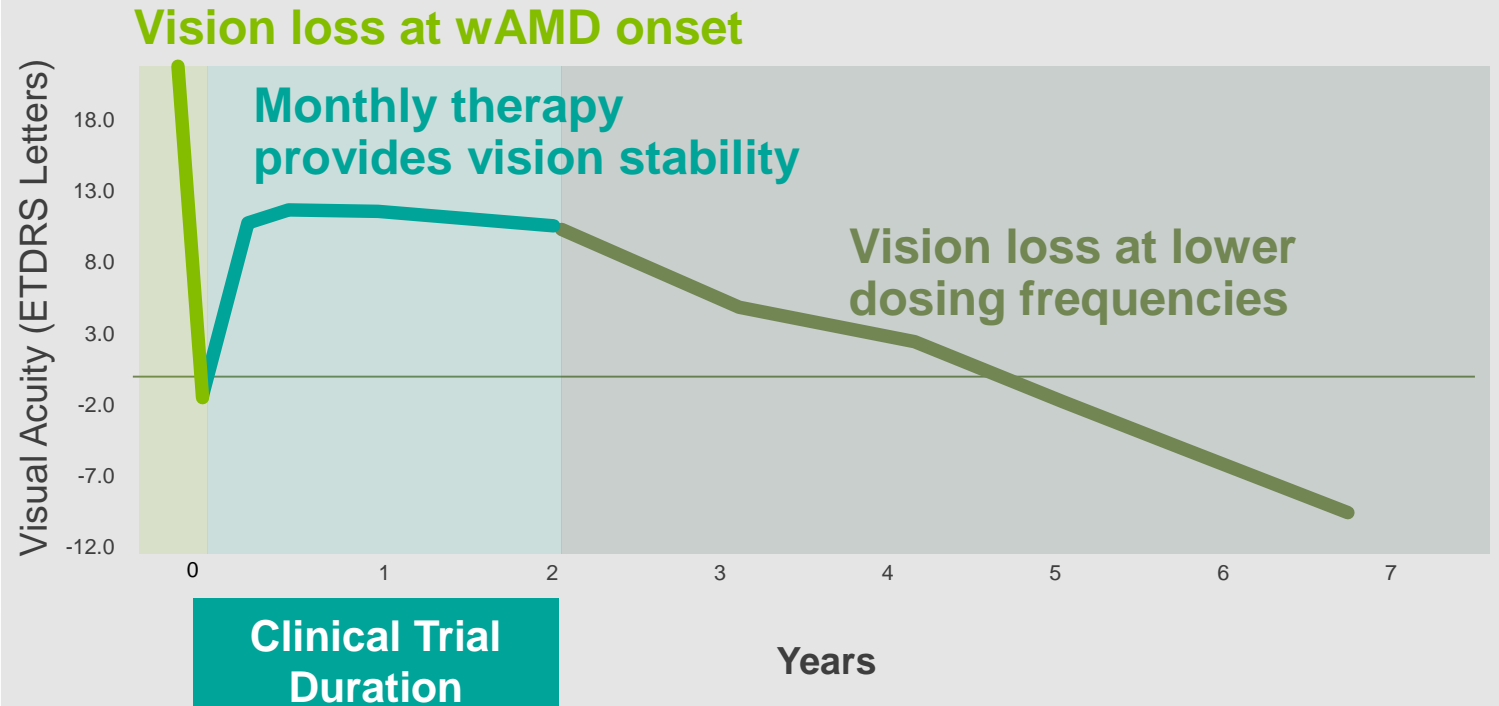
- › Vision loss from abnormal blood vessel proliferation and leakage due to VEGF activity
- › 1.2M U.S. patients¹, 3M globally
- › \$8B global sales for anti-VEGF proteins
- › Challenging compliance
 - Need for monthly/every other month intravitreal injections
 - Vision loss from underdosing

Significant Opportunity to Improve wAMD Treatment

Compliance with Monthly Injections is Difficult



Poor Compliance Leads to Vision Loss²



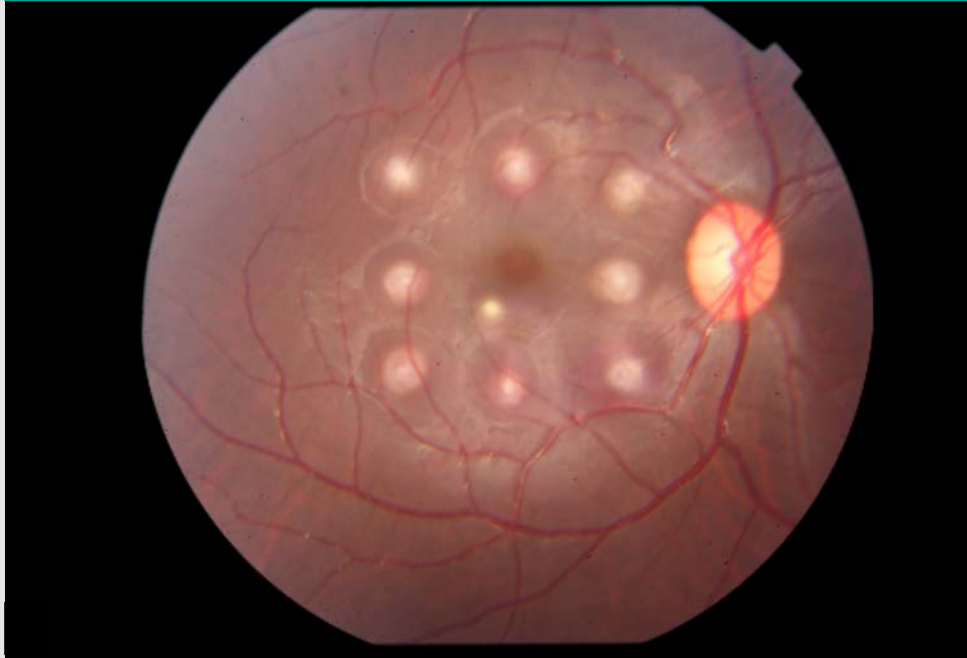
Potential to Treat wAMD with a Single Intravitreal Injection



- › **Intravitreally-delivered** gene therapy, ADVM-022, showed durable anti-VEGF expression in pre-clinical proof-of-concept studies
 - **Injection avoids subretinal surgery**
- › **ADVM-022** (AAV.7m8-aflibercept) advancing
 - Robust protein levels seen in vitreous up to 52 weeks post injection

Industry-standard Model Used to Test New wAMD Therapies

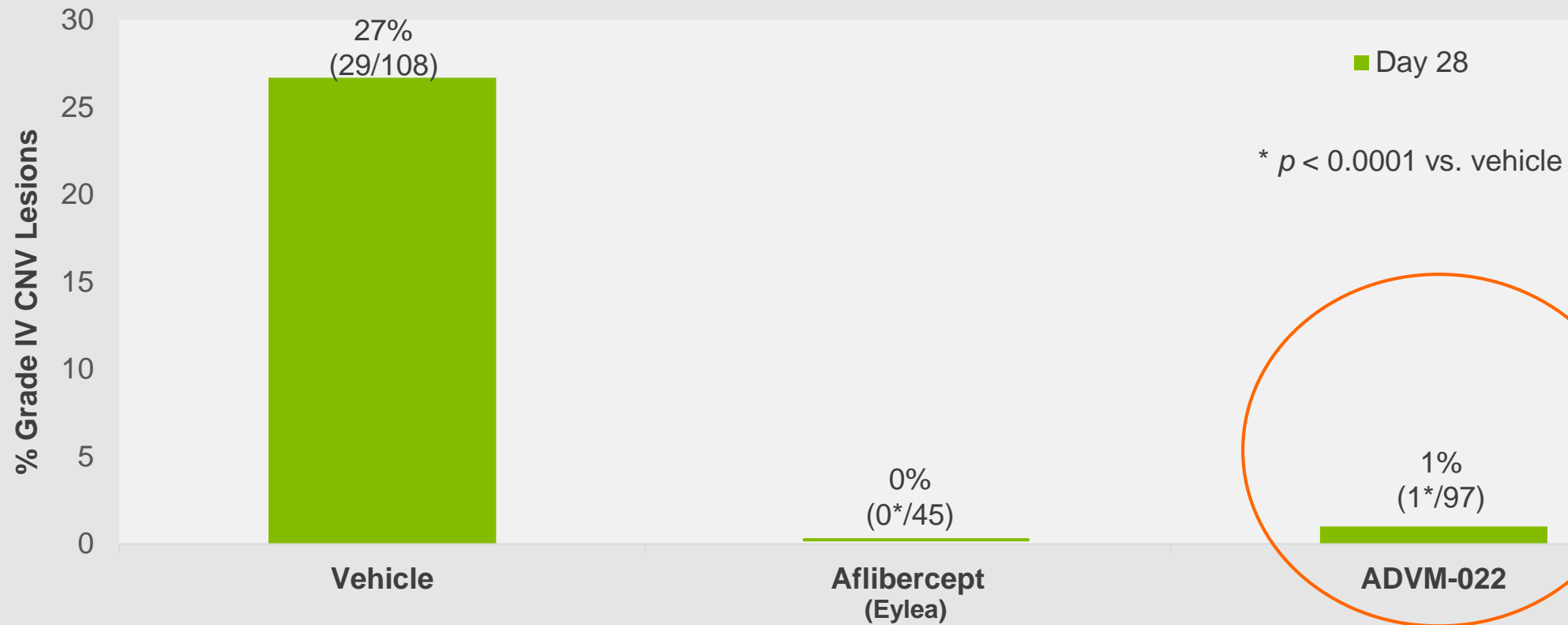
Retinal Image after Laser Treatment



- › Choroidal neovascularization (CNV) is induced experimentally by laser
- › Nine lesions per eye are graded for severity (grades I-IV)
- › Efficacy is assessed by reduction of the number of most severe, clinically relevant (grade IV) lesions

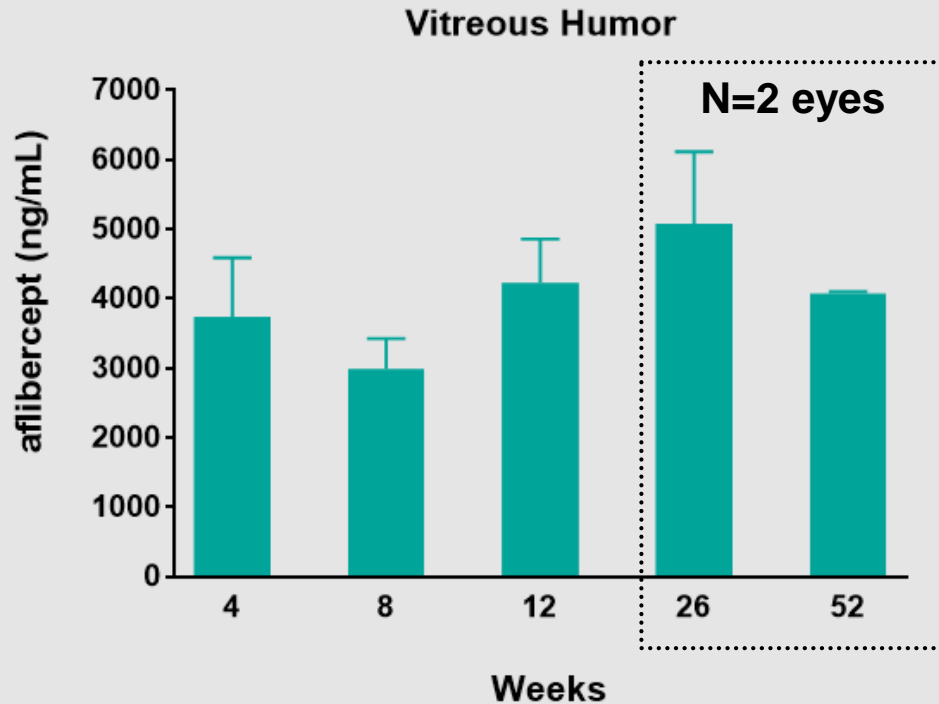
Single Injection ADVM-022: 28-Day Efficacy Comparable to Positive Control

ADVM-022 (AAV.7m8-aflibercept)

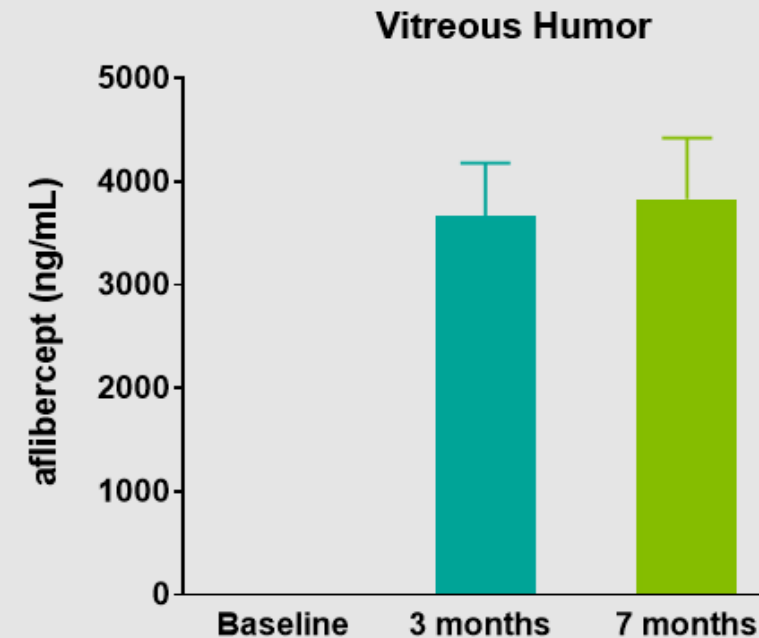


Robust and Sustained Aflibercept Levels Detected in Vitreous up to 52 Weeks after Single Injection ADVM-022

ADVM-022 NHP Study 1
(2×10^{12} vg/eye, n=2-4 eyes*)



ADVM-022 NHP Study 2
(2×10^{12} vg/eye, n=14 eyes)



Advancing Intravitreally-delivered ADVM-022



Next steps

- › Held pre-IND meeting with FDA in 1Q17
- › Evaluating durability of anti-VEGF protein expression in NHPs
 - Durable expression seen out to 7 months in 14 eyes
 - Expect to report efficacy at 12 months in 1H18
- › Planning to file IND in 2H18

Industry-leading Capabilities in Novel Vector Development



Adverum's Research Initiatives

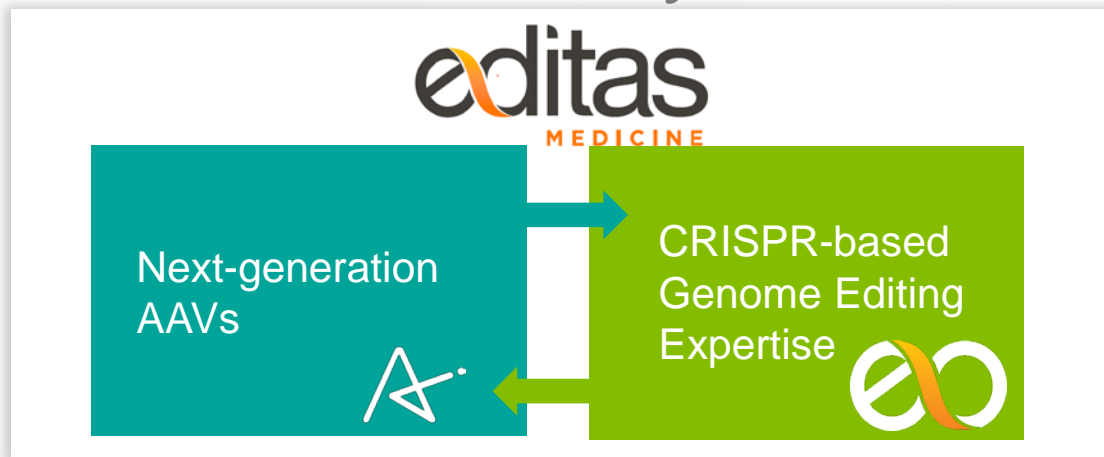
- › Research to engineer next-generation vectors
 - Directed evolution and rational design of AAV capsids
 - Potential for better transduction efficiency, antibody neutralization profiles
- › Discovery of improved ubiquitous and cell-specific promoters, expression cassettes
 - Potential for optimal transgene expression upon transduction in target tissue
 - Opportunity to decrease off-target effects
- › Production of sufficient high-throughput libraries for screening in large animal studies
- › Development of novel expression cassettes

Adverum's In-house Manufacturing Expertise Derisks Process to Support Clinical and Commercial Product Supply

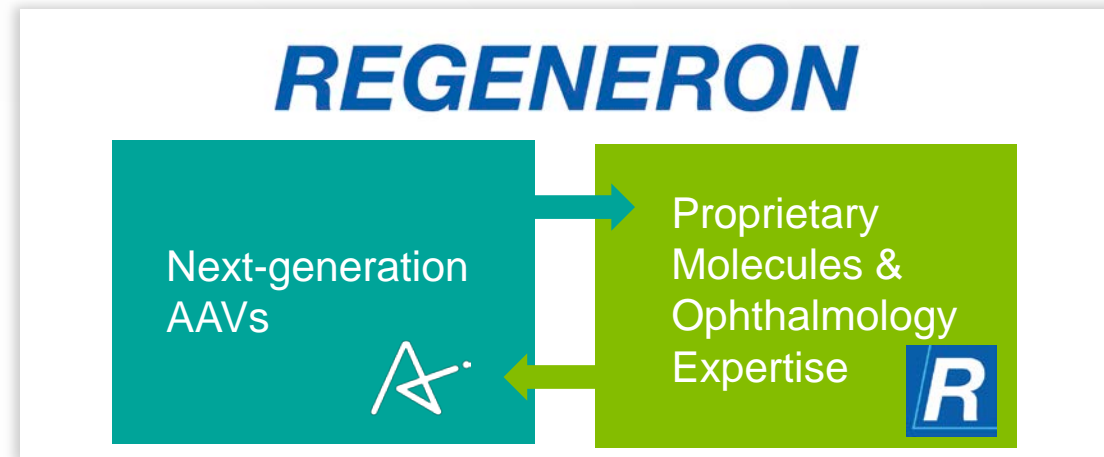


- › Process development capabilities to deliver scalable process to GMP contract manufacturer
 - Baculovirus/Sf9 production system applicable to multiple AAV serotypes
 - State-of-the-art bioindustry technology for purification
 - Process is readily transferred to CMO
- › Assay development capabilities and GMP quality control to optimize product release for human use

Adverum's Leadership in Ophthalmic Vector Development, Product Delivery Has Led to Collaborations






- › Up to 5 ophthalmic indications
- › CRISPR technology delivery
- › \$1M upfront* to evaluate next-generation AAV vectors
- › \$1M option exercise fee for each indication
- › Up to a mid-teen, million-dollar amount in development and commercialization milestones for each product
- › Tiered royalties from mid-single digits to low-teens on net sales of each product



- › Up to 8 ocular therapeutic targets (4 already identified)
 - AVA-311 for juvenile X-Linked Retinoschisis (XLRS) as first collaboration program
- › Adverum has option to share up to 35% on profits and development costs for two targets
- › \$8M initial payment, up to \$640M in payments upon achievement of milestones, low to mid-single digit royalties on WW net sales
- › Initial 3-year collaboration term recently extended by additional 3 years to May 2020

Leadership Team: Significant Clinical Development Experience

Name	Background	Experience
Amber Salzman, Ph.D. President and CEO	25+ years experience in pharma and biotech management with 15+ years leading gene therapy and rare disease initiatives	
Leone Patterson Chief Financial Officer	20+ years experience in management and financial operations	
Athena Countouriotis, M.D. SVP, Chief Medical Officer	15 years experience leading drug development programs with several successful approvals, orphan oncology experience	
Mehdi Gasmi, Ph.D. Chief Science and Technology Officer	20+ years experience developing gene therapy vectors for the treatment of common and rare diseases	
Jennifer Cheng, Ph.D., J.D. VP and General Counsel	15+ years experience in biotechnology companies, including legal and intellectual property counsel and research	

Upcoming Milestones



ADVIM-043 for A1AT Deficiency

- ✓ Began patient enrollment in ADVANCE Phase 1/2 clinical trial 4Q17
- Expect to report preliminary data from ADVANCE trial 2H18

ADVIM-022 for wAMD

- Expect to report 12-month efficacy data from ongoing preclinical NHP study 1H18
- Plan to file IND 2H18

ADVIM-053

- Plan to file IND 2H18

\$187M cash* to fund development of 3 leading programs End of 2019

* \$187M in cash, cash equivalents, and marketable securities as of September 30, 2017
45.0M shares outstanding as of October 31, 2017



ADVERUM
BIOTECHNOLOGIES

Nasdaq: ADVM