Delivering Scalable, Cost-Effective, Mass-Market Gene Therapy to Patients with Significant Unmet Needs

American Pharma Manufacturing and Outsourcing Summit 2025

R. Andrew Ramelmeier, PhD, CTO
November 2025

ADVERUM

- Limited Market Size (Rare Diseases)
- Limited Patient Access
- Inefficient Platforms and Scalability Challenges
- High Unit Costs driven by high COGs and Doses
- Redosing vs Potential for a cure

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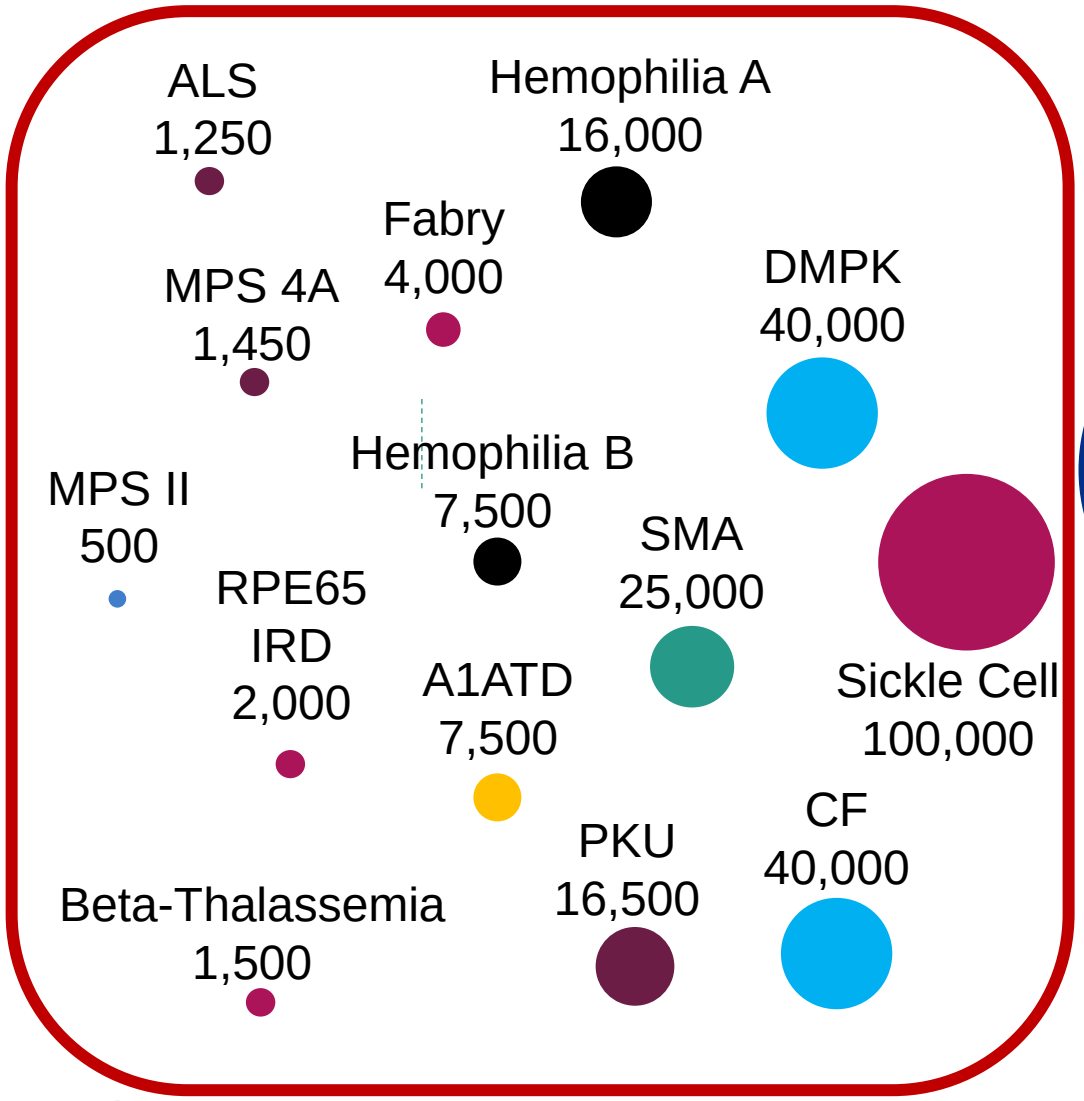
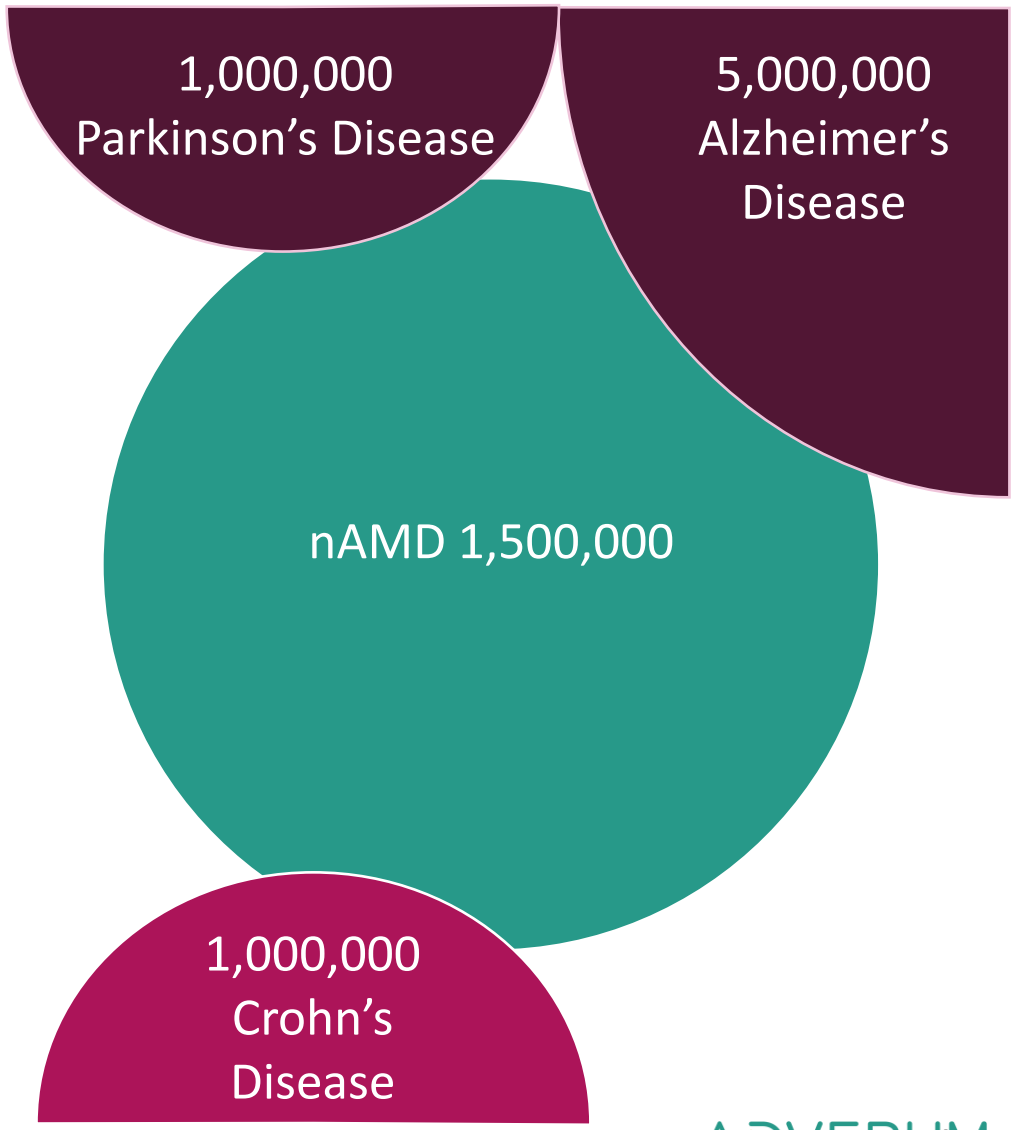
Rare Diseases > 10k





Disk size approximately proportional to US figure; figures indicate an incidence

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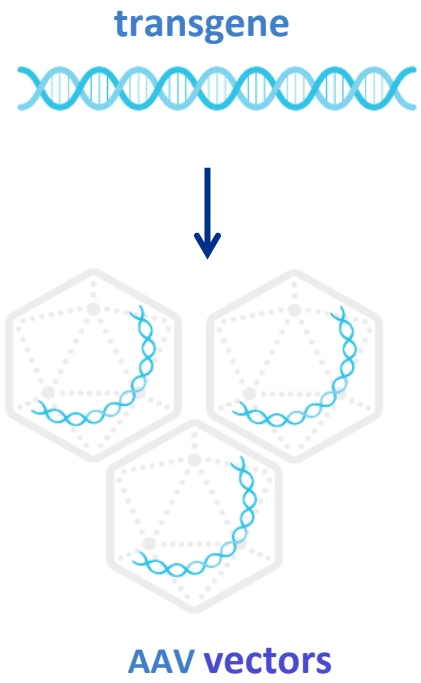
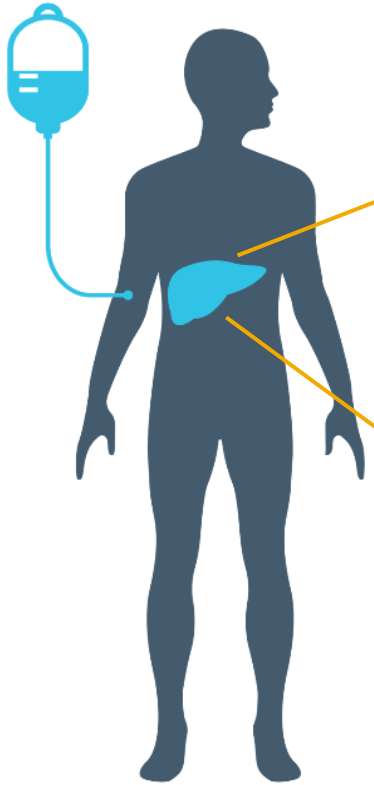
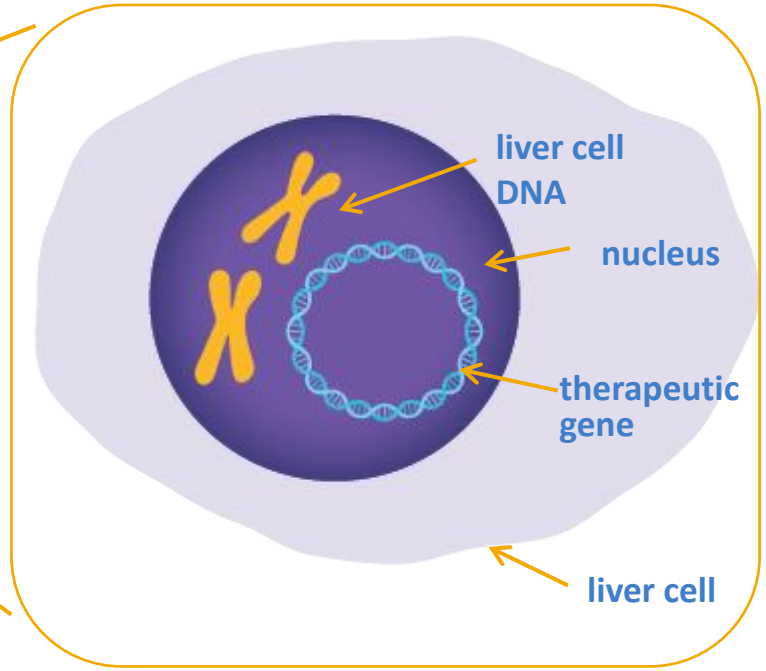
Packaging into AAV vectors



IV Delivery*



In the Liver



*Administered at specialized gene therapy centers

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From Peter Marks,
former Director CBER, FDA

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Market price for approved AAV gene therapies[1]

Gene therapy	Approval year	Mfg system	Disease	Dose[2]	Price per dose[3] ($)
Roctavian®	2024	Sf9 insect cells	hemophilia A	6E13 vg/kg	2,300,000
Hemgenix®	2022	Sf9 insect cells	hemophilia B	2E13 vg/kg	3,500,000
Zolgensma®	2019	HEK 293 human cells	spinal muscular atrophy (SMA)	1.1E14 vg/kg	2,100,000
Luxturna®	2017	HEK 293 human cells	RPE65 inherited retinal dystrophy	1.5E11 per eye	425,500 (per eye)

How much to manufacture these AAV therapies?

- Depending on cell system and titers, COGs can be $100,000s of dollars per dose
- With new developments in these production systems, COGs <$100k per dose are expected

1. The estimated annual financial impact of gene therapy in the United States, Chi Heem Wong et al, *Gene Therapy* volume 30, pages761–773 (2023) 2. Dose can be > 1E15 per patient for IV administration
3. For a patient weighing 70 kg; Alaa Alshehri et al., Journal of Managed Care & Specialty Pharmacy, Volume 30, pages 1065-1195 (2024)

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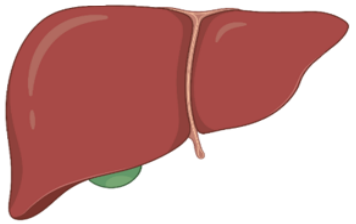
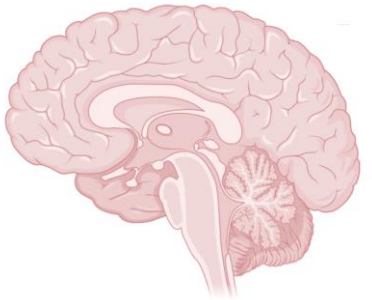
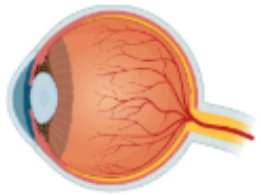
- Many of the current gene therapy target the liver, which constantly renews itself; at most, a liver cell will survive 10 years.
- Gene therapy targeting the liver will need to be re-dosed. Neutralizing antibodies will interfere with that re-dosing.
- Ideally for a potential cure, gene therapy should target cells and tissues that do not regenerate, such as within the brain, spinal cord, heart muscle, the ear and the eye.
- Or use gene editing to target a patient's DNA to recover permanently the functions of critical proteins







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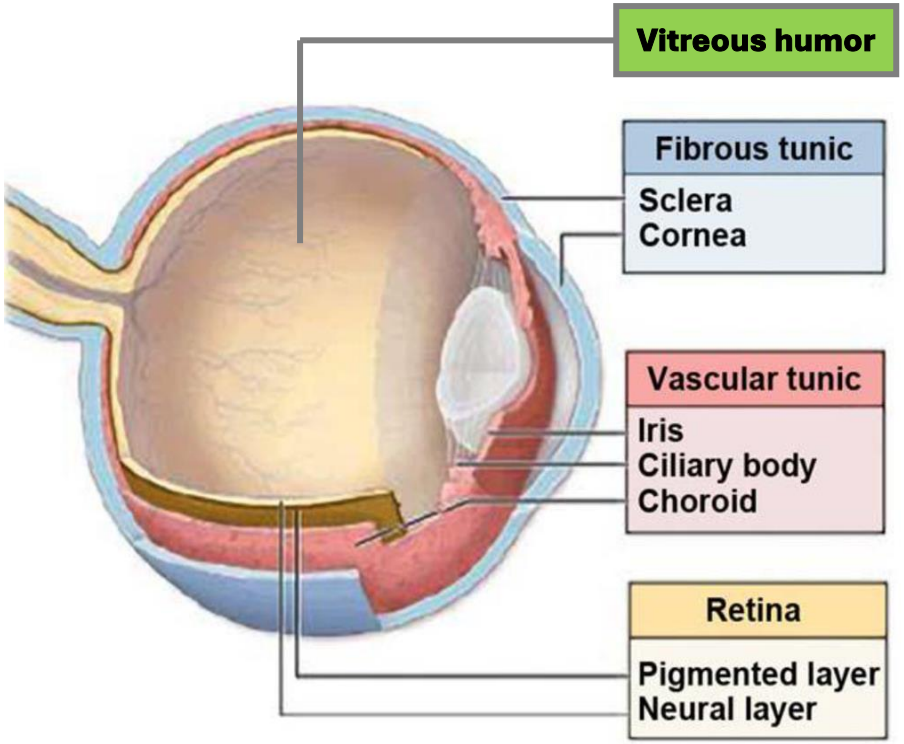
- The eye is small and compartmentalized requiring low doses and favoring viral-mediated gene therapy
- Some eye cells, particularly in the retina, do not regenerate so a gene vector there theoretically could last a lifetime
- In 2017 LUXTURNA® became the first approved gene therapy in the US as a treatment for an inherited retinal disease
- >100 active investigational gene therapy clinical trials in ophthalmic diseases to potentially treat millions of patients, including wet AMD



Drag, Selina et al. "Gene Therapy for Retinal Degenerative Diseases: Progress, Challenges, and Future Directions." *Investigative ophthalmology & visual science* vol. 64,7 (2023): 39. doi:10.1167/iovs.64.7.39

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Globally, the leading causes of vision impairment and blindness are:

Age-related macular degeneration
Geographic Atrophy
Diabetic retinopathy
Cataract
Glaucoma
Refractive errors

Steinmetz, Jaimie D, et al. "Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to Vision 2020: The right to sight: An analysis for the global burden of disease study." The Lancet Global Health, vol. 9, no. 2, Feb. 2021, https://doi.org/10.1016/s2214-109x(20)30489-7.

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Wet Age-Related Macular Degeneration

A leading cause of vision loss among older adults

1.5M
US Patients

20M
Worldwide

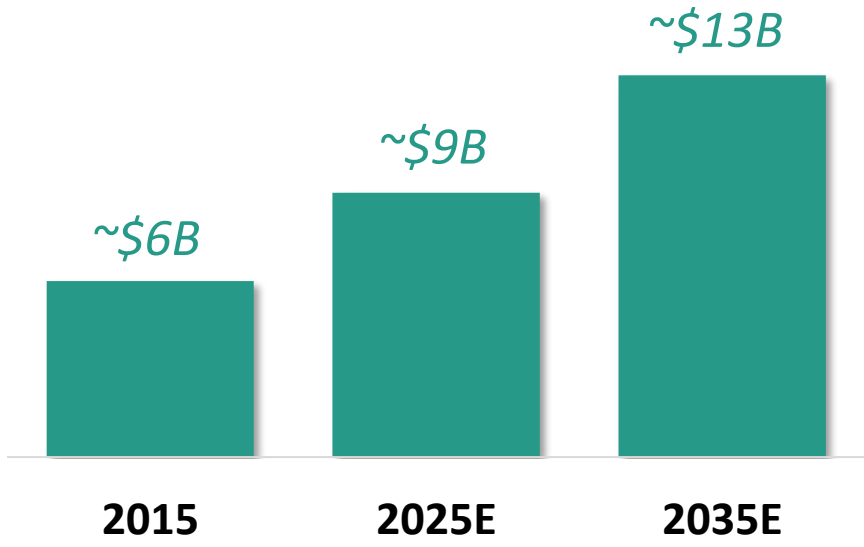
~200K US patients diagnosed annually

Up to 42% of patients develop bilateral disease within 2-3 years of initial diagnosis

Multi-Billion Dollar Market Opportunity

Growth driven by aging population and product innovation

Global Wet AMD Sales



Sources: Bright Focus Foundation. Age-Related Macular Degeneration: Facts & Figures.; Wong WL, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health. 2014;2:106–16.; Gangnon RE et al. (2015) JAMA Ophthalmol; 133 (2): 125–132.; 2023 Cowen Equity Research – Therapeutic Categories Outlook.; Company estimates based on Cowen figure for 2025E, epidemiology and primary market research conducted by a third party on behalf of Adverum

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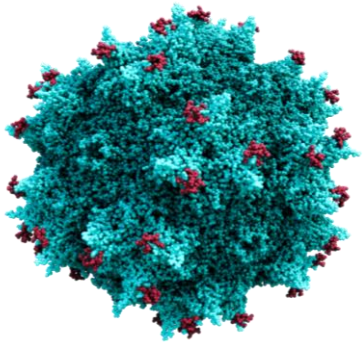
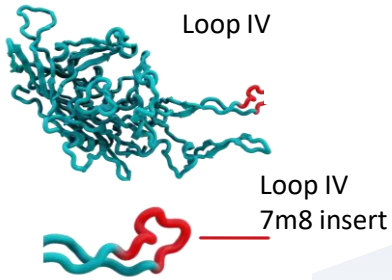
AAV.7m8



AAV.7m8 monomer



Ixo-vec

Gene therapy designed to preserve vision with a single intravitreal injection

AAV.7m8: Created by Directed Evolution

Single clinically routine in-office injection

Gold standard vector for IVT gene therapy

Transgene encoding aflibercept, a clinically validated anti-VEGF protein

Biofactory approach for durable therapeutic levels

AMD, age-related macular degeneration; IVT, intravitreal.

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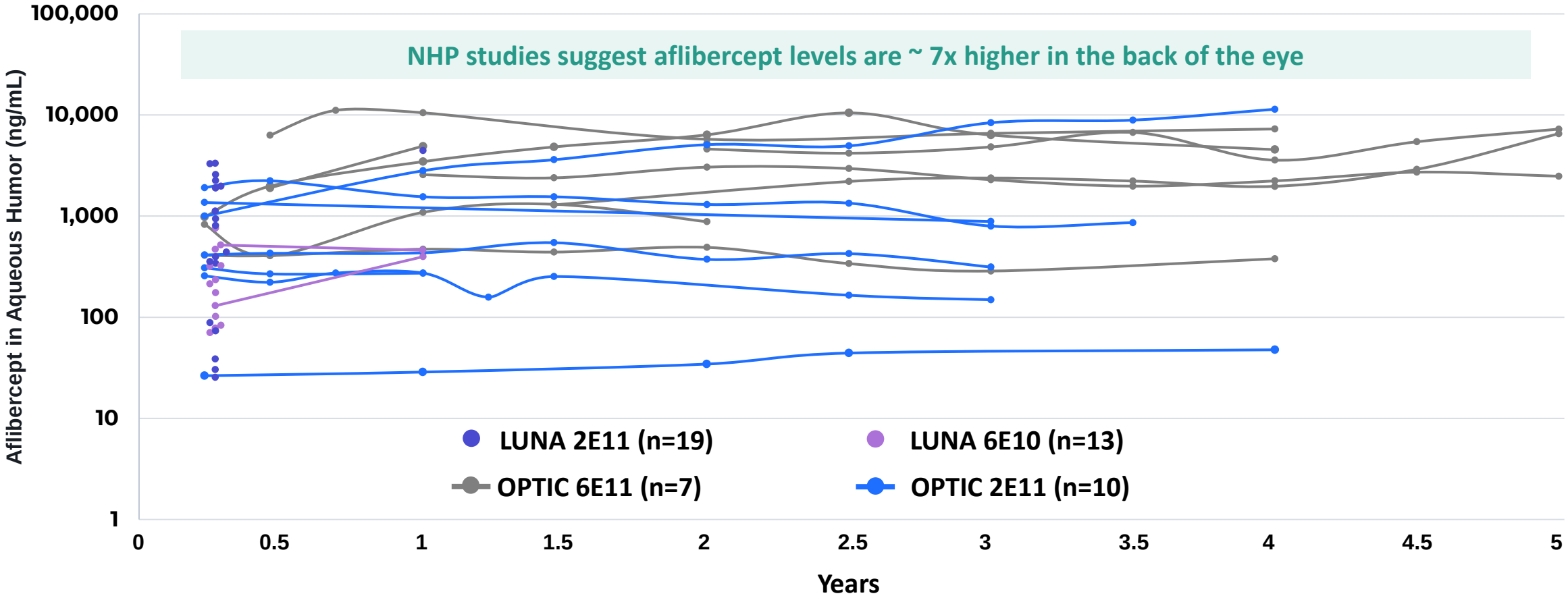
Early aflibercept levels are associated with sustained long-term protein expression



In OPTIC, all subjects tested had quantifiable aqueous humor aflibercept levels (one subject had levels above and below the limit of quantification of the assay [25 ng/mL] at multiple time points).
In LUNA, 32 of 38 subjects (84%) had quantifiable aqueous humor aflibercept levels; the patients who had aflibercept concentrations measured below the limit of quantification (BLOQ) included patients at both doses who remained injection free or experienced treatment burden reduction. Measurements BLOQ of the assay or within 8 weeks of supplemental aflibercept injections are not shown. LUNA revised to stop collection of AH samples. NHP data: Kiss, Szilárd et al, Molecular Therapy Methods & Clinical Development, Volume 18, 345 - 353

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DATA CUT-OFF: OPTIC 21AUG2024, LUNA 29AUG2024

ADVERUM BIOTECHNOLOGIES

First IVT AAV Platform Developed via *in vivo* Directed Evolution

*AAV.7m8 capsid is gold standard for ocular transduction**

First Clinical Administration of IVT Gene Therapy for Mass Market Indication

First company to successfully advance an IVT gene therapy for retinal disease to the clinic

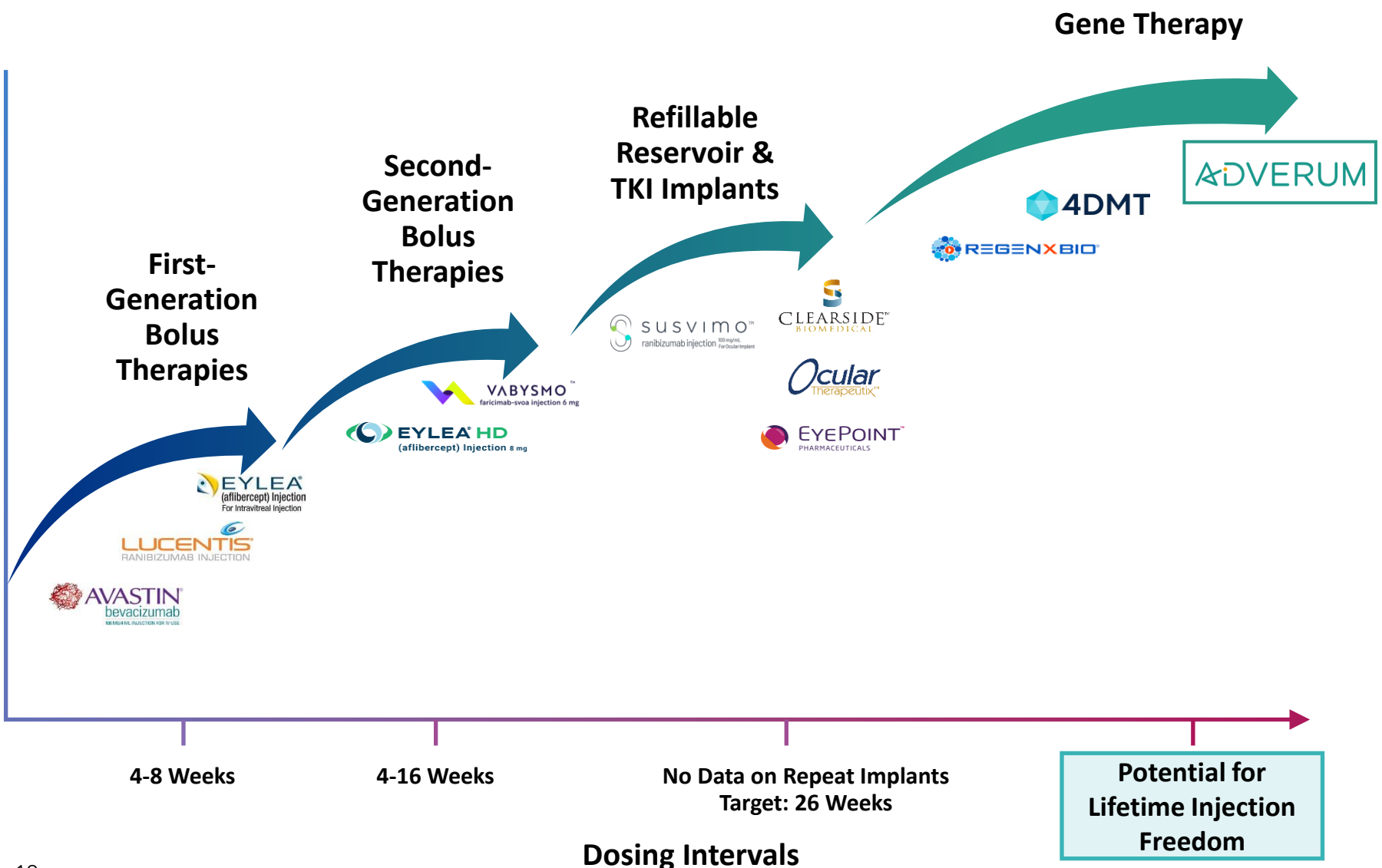
First To Show Multi-Year Durability From Single IVT Injection

OPTIC study demonstrated sustained aflibercept levels through 5 years

Strong Clinical Momentum

- Phase 3 Wet AMD program in a broad patient population ongoing
- First IVT gene therapy to complete screening for Phase 3 study
- Granted RMAT designation by FDA, PRIME designation by EMA

**Validated in 3 clinical programs. AAV, adeno-associated virus; AMD, age-related macular degeneration; IVT, intravitreal; RMAT, Regenerative Medicine Advanced Therapy.*



Ixo-vec:

Designed to deliver stable, continuous local aflibercept production

Potential for:

- Reduced treatment burden
- Life-long vision preservation
- Sustained aflibercept mitigates patient drop-off

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The Largest Unmet Need in Wet AMD Treatments[1]

65%

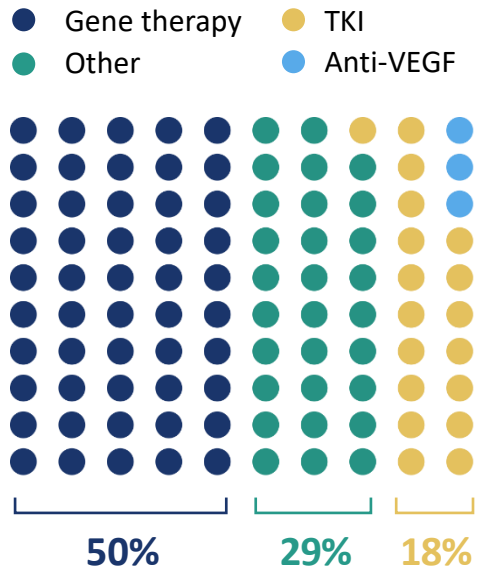
of Physicians Identified Greater Durability as the Largest Unmet Need

Broad consensus among retina specialists on the need for more durable treatments

Gene Therapy Identified as the Most Promising Emerging Therapy in Wet AMD[1]

50%

Identified Gene Therapy as the Most Promising Emerging Therapy



Retina physicians believe in the transformative potential of gene therapy for patients with wet AMD

1.Hahn P, ed. ASRS 2025 Preferences and Trends Membership Survey. Chicago, IL. American Society of Retina Specialists; 2025 (N=987). TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

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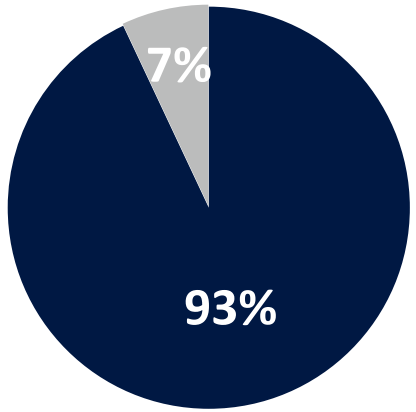
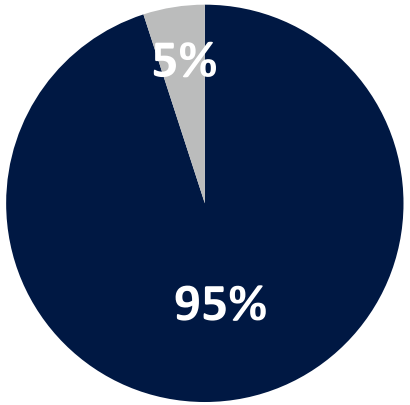
Would you prefer Ixo-vec over the prior treatment(s)?



Total Study
(n=56)

Would you want Ixo-vec in your other eye if you bilateral AMD?



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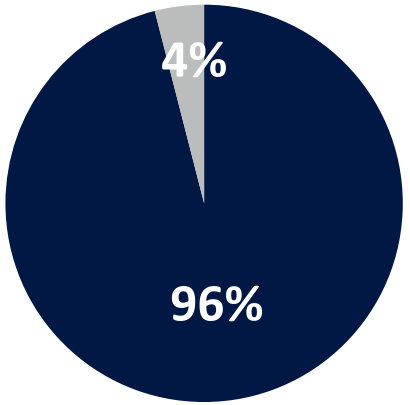
Would you recommend Ixo-vec to your family or friends?



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Yes No

Adverum conducted a pre-specified Patient Preference Survey in LUNA

Data cut: LUNA 29AUG2024

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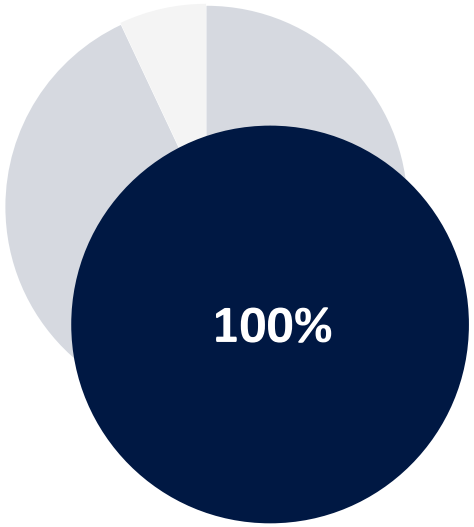

6E10 + Difluprednate
(n=10)

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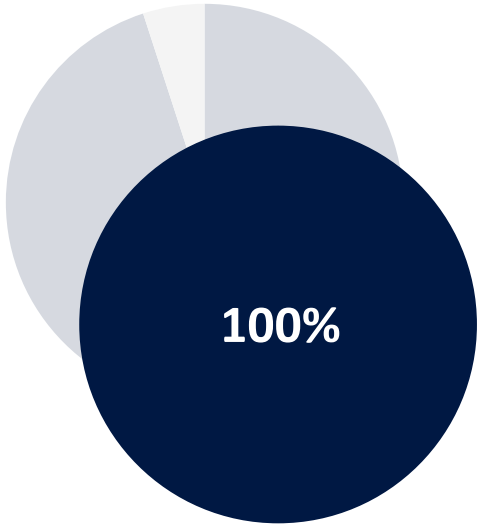

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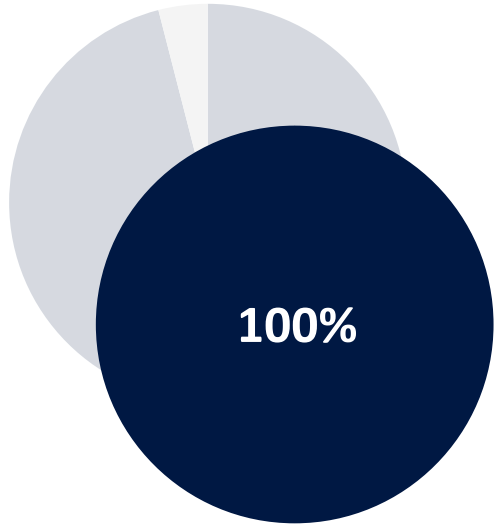

6E10 + Difluprednate
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Yes No

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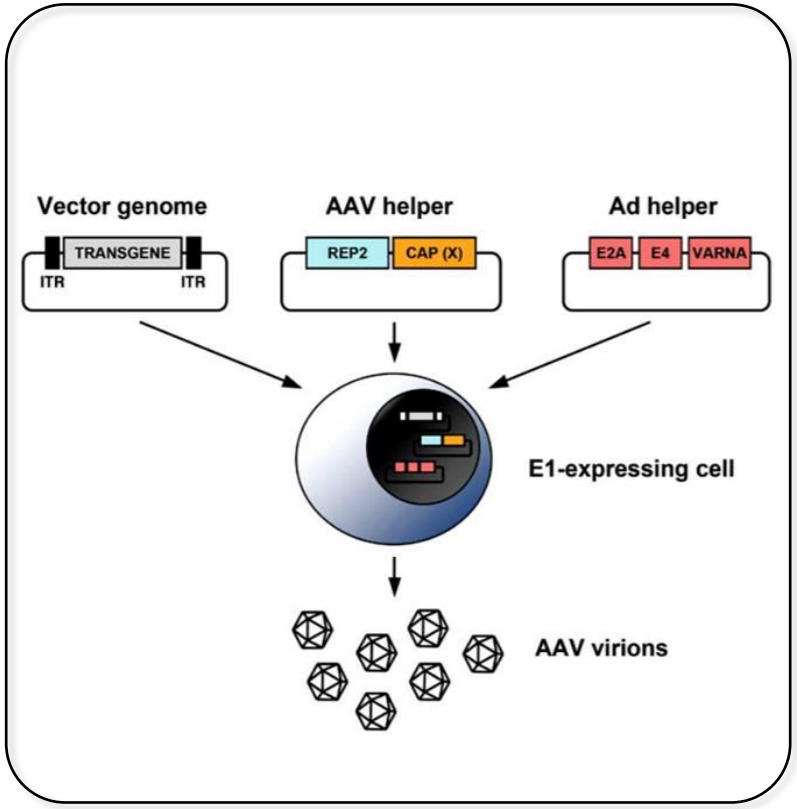
Data cut: LUNA 29AUG2024

Ixo-vec is an investigational therapy and has not been approved by the FDA for any use

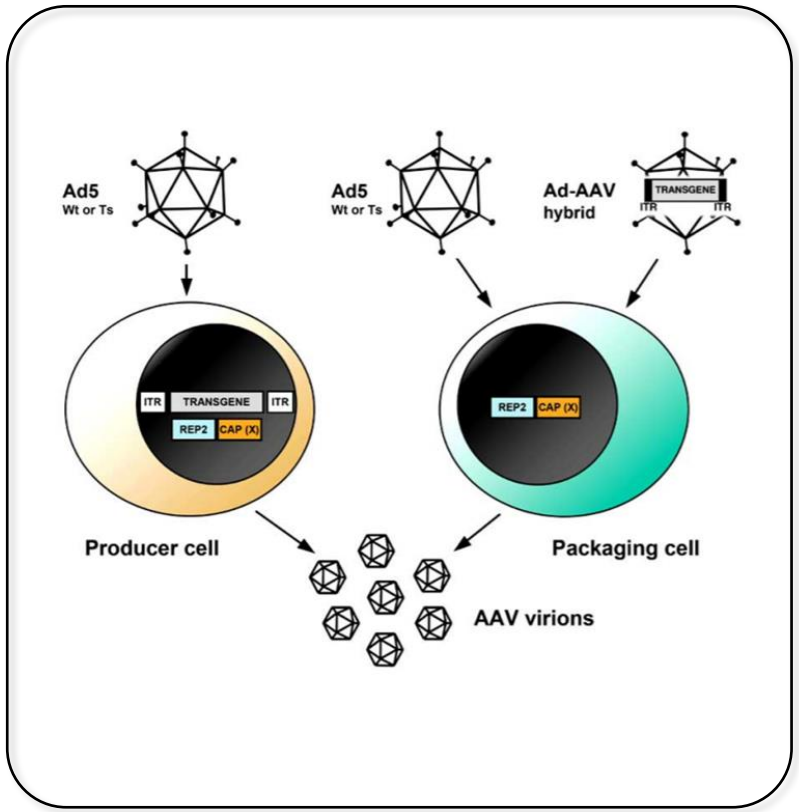
Key CMC considerations

- Stable and efficient production systems to make AAV
- Ability to make hundreds of thousands of doses, annually
- Reasonable manufacturing costs
- Robust CMC strategy for commercial readiness
- Leverage Commercial-scale manufacturing expertise and capacity at global CDMO

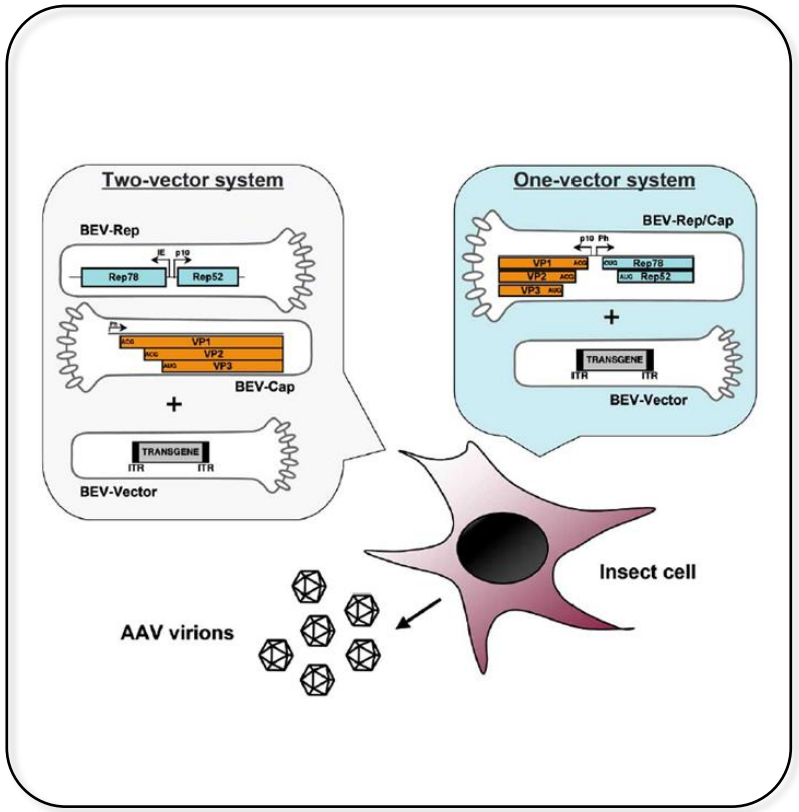
Triple Transfection
HEK 293 w/plasmids



Producer/Packaging Cell Line



Sf9/Baculovirus



Eduard Ayuso, et al. Current Gene Therapy, 2010

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	Triple Transfection HEK 293 w/plasmids	**Sf9/Baculovirus**
Titer (vg/L)	~1E+14	~1E+15 (10x better than HEK)
Scalability	Low (adherent) Medium (suspension)	High
Raw material cost	High (many plasmids, lots)	Low
Speed to clinic	Fast	Slow/Medium
Potency	High	Low/medium
% Full capsid at Harvest	Low (<<50%)	Medium/High (>50%)
Safety concern	adventitious agents (human viruses)	rhabdovirus clearance

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IVT Gene therapy for wet AMD involves a very small dose

- At 6E10 vg per eye versus >1E13 vg/kg patient (>1E15 vg total) for systemic IV therapies
- Most efficient production system will ensure best COGs
- 6E10 dose could translate to a COGs 1000-fold lower per dose, per eye for highly prevalent indication – critical to address millions of patients who have wet AMD globally

- **Established a robust process early in development (Phase 1-2) and target commercial process and analytics at Phase 3**
- **Cost-efficient Sf9 suspension process and low dose enables very effective COGS**
- **Commercial-scale manufacturing at global CDMO, analytics developed and testing in-house**
- **Supported by robust regulatory CMC input**

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Thank You!

Acknowledgments:

- Nicole Wood
- Erin Carlson
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- Pauravi Gandhi
- Ken Glasscock

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