Ixoberogene soroparvovec (Ixo-vec) Intravitreal Gene Therapy for Neovascular Age-Related Macular Degeneration

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Disclosures

- **Adverum Biotechnologies** – Consultant/Advisor, Equity
- Regenxbio – Consultant/Advisor, Equity
- Genentech/Roche – Consultant/Advisor
- Fortress Bio – Consultant/Advisor, Equity
- Optos – Consultant/Advisor, Research grant support
- Novartis – Consultant/Advisor
- Intellectual Property related to gene and cellular therapy – assigned to Weill Cornell/Cornell University

OPTIC Study: 2-Year Safety and Efficacy of Ixo-vec for nAMD

OPTIC Gene Therapy in nAMD

Primary Objective

- Assess the safety and tolerability of a single IVT injection of Ixo-vec

Secondary Objective

- Evaluate vision maintenance (BCVA)
- Evaluate anatomy (SD-OCT)
- Assess the need for supplemental therapy

	Prophylaxis Steroid Regimen
Cohort 1 (n=6) 6 x 10^{11} high dose	Oral*, 13d
Cohort 2 (n=6) 2 x 10^{11} low dose	Oral*, 13d
Cohort 3 (n=9) 2 x 10^{11} low dose	Eye Drops**, 6 wks
Cohort 4 (n=9) 6 x 10^{11} high dose	Eye Drops**, 6 wks

Supplemental Aflibercept (2 mg IVT) Criteria:

1. Loss of ≥10 letters in BCVA (ETDRS) from baseline that is attributed to intraretinal or subretinal fluid observed by the investigator
2. Increase in central subfield thickness >75 µm from baseline
3. Presence of vision-threatening hemorrhage due to AMD

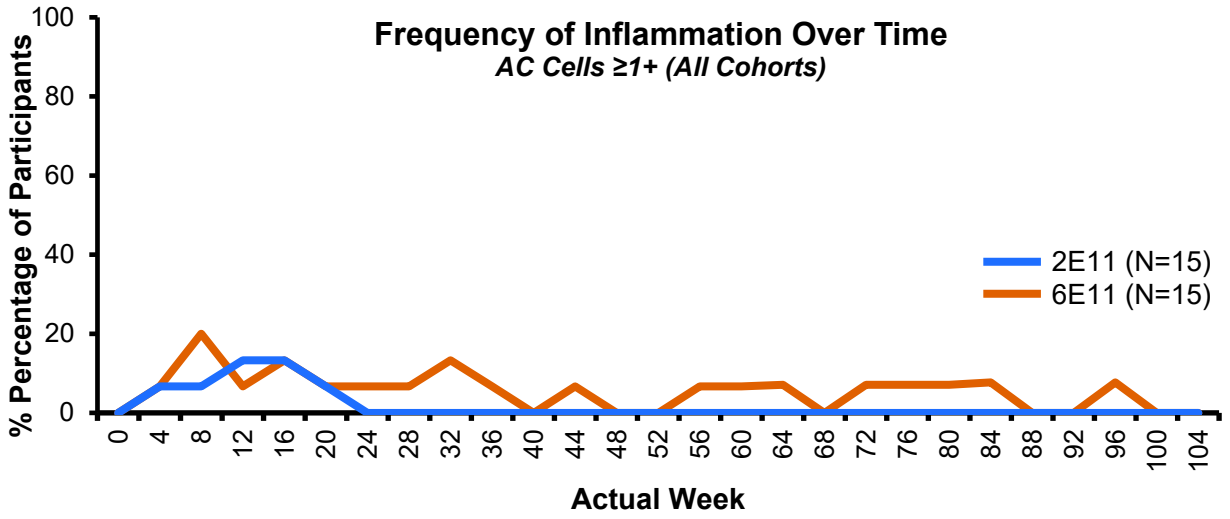
**Subjects received prophylaxis of 60 mg oral prednisone for 6 days starting at Day –3 followed by 7-day taper. **Subjects received prophylaxis of QID difluprednate eye drops for 3 weeks starting at Day 1 followed by a 3-week taper.*
Final analysis includes all participants regardless of baseline neutralizing antibody titer.
AAV, adeno-associated virus; AMD, age-related macular degeneration; BCVA, best corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; IVT, intravitreal therapy; QID, four times daily; SD-OCT, spectral domain optical coherence tomography; NCT03748784.

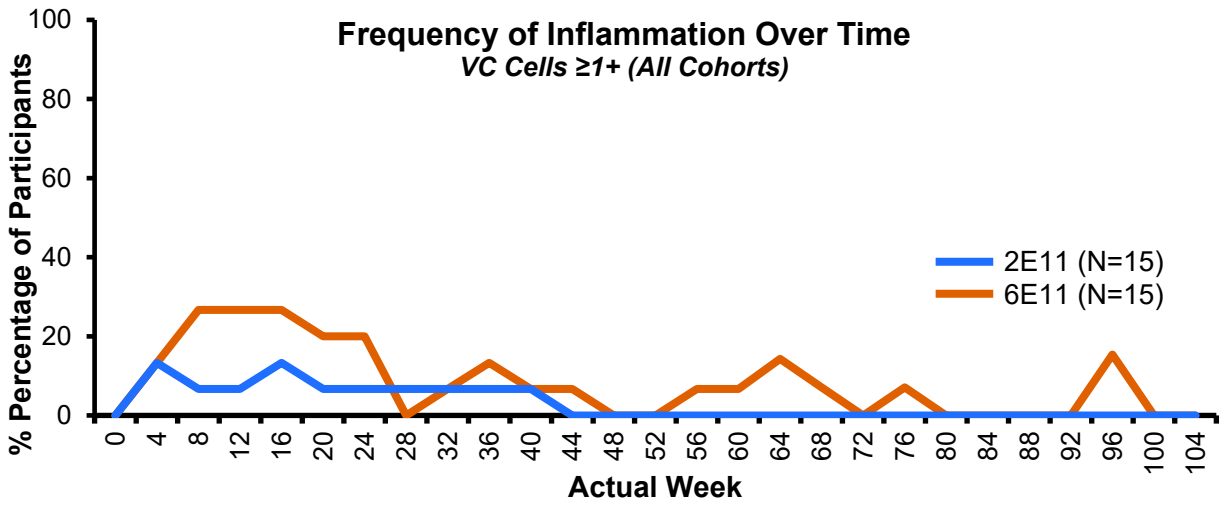
Final 2-Year Analysis

Ixo-vec OPTIC Study Safety Summary

- Despite short corticosteroid prophylaxis, Ixo-vec was generally well tolerated. The most common AE was dose-dependent, mild to moderate inflammation responsive to topical corticosteroids
- At Year 2, inflammation at the 2×10^{11} dose resolved, and no participants required corticosteroids
- Across all cohorts, most Ixo-vec-related ocular AEs were mild (83.7%) to moderate (15.6%)
- Most commonly reported ocular AE was anterior chamber cell
- Two Ixo-vec related SAEs were reported: uveitis (responsive to topical corticosteroids) and dry AMD
- No vasculitis, retinitis, choroiditis, vascular occlusions, endophthalmitis, or clinically relevant low IOP events were observed at either dose

Frequency of Inflammation Decreases Over Time





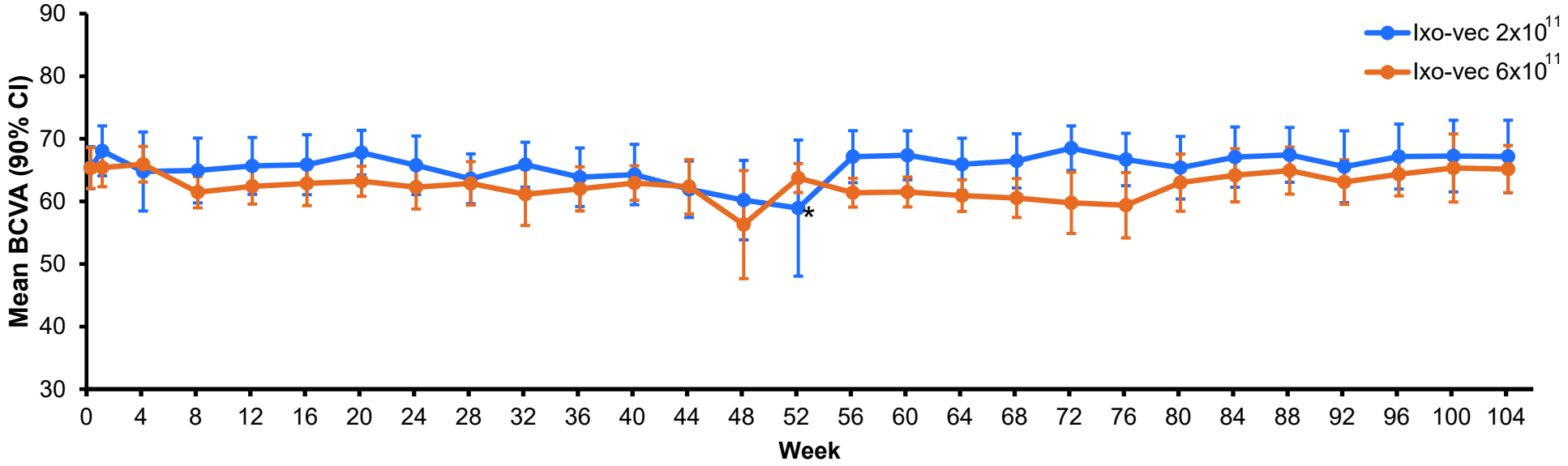
AC, aqueous cells; AE, adverse event; SAE, serious adverse event; VC, vitreous cells.

Final 2-Year Analysis

Ixo-vec Maintains or Improves BCVA and CST Through 2 Years

OPTIC Gene Therapy in nAMD

Mean BCVA (90% CI) by Cohort and Week

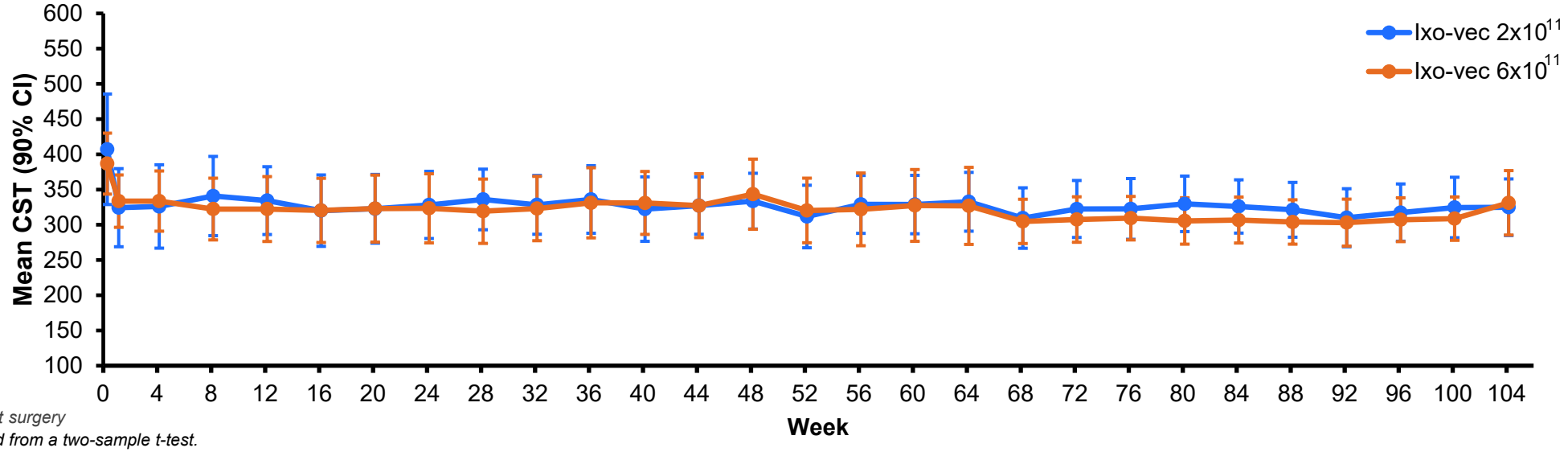


Mean BCVA (letters) change from baseline to last visit (90% CI)

+0.2 (-4.6, 5.0)
2x10^11 vg/eye

-0.2 (-3.4, 3.0)
6x10^11 vg/eye

Mean CST (90% CI) by Cohort and Week



Mean CST (µm) change from baseline to last visit (90% CI)

-60.2 (-99.1, -21.3)
p = 0.017**
6x10^11 vg/eye

-92.9 (-153.3, -32.6)
p = 0.017**
2x10^11 vg/eye

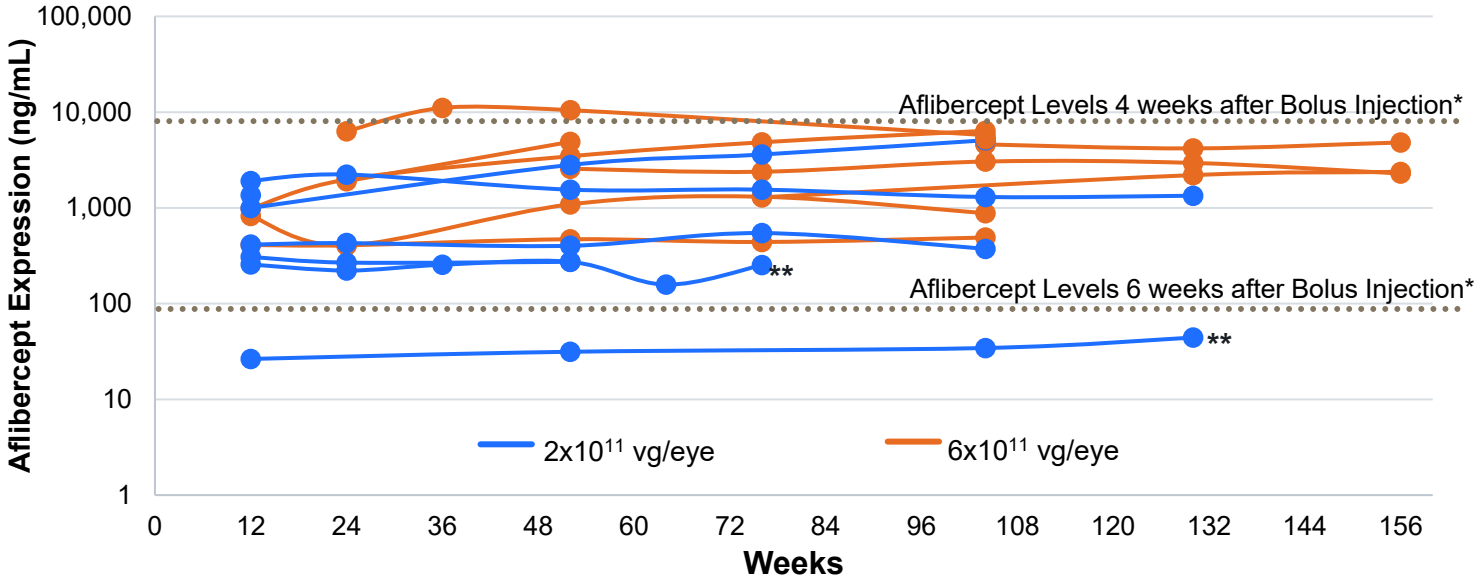
**Cataract surgery*
***Derived from a two-sample t-test.*

Final 2-Year Analysis

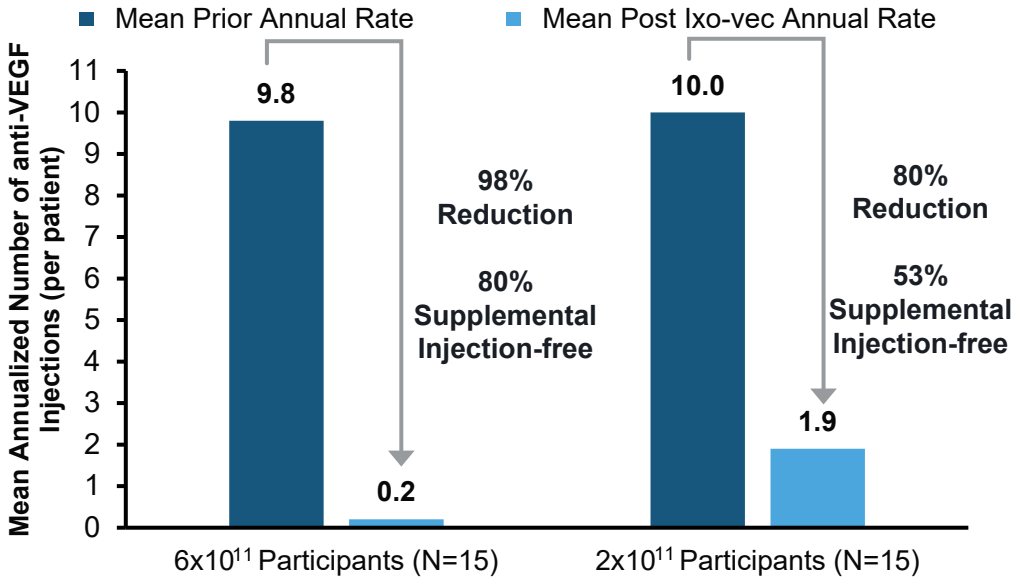
Continuous Aflibercept Protein Expression Following Ixo-vec Resulted in a Clinically Relevant Reduction in Annualized Anti-VEGF Injections

OPTIC Gene Therapy in nAMD

Aflibercept Expression - Individual Participant Plots



Reduction in Annualized Anti-VEGF Injections



*Modeled based on Do et al. Retina 2020; 40:643-647.
** Participant received supplemental aflibercept injections
Protocol amendment for aqueous sample collection for participants that consented. To isolate the effect of Ixo-vec, samples that were collected within 2 months of supplemental aflibercept are not shown.
Annualized rate (Prior) = (number of IVTs in 12 months prior to Ixo-vec) / (days from the first IVT in the past 12 months to Ixo-vec / 365.25).
Annualized rate (Post) = (numbers of aflibercept IVTs since Ixo-vec) / (days from Ixo-vec to the last study follow-up / 365.25).
VEGF, vascular endothelial growth factor.

Final 2-Year Analysis

Ixo-vec OPTIC 2-Year Study Conclusions

- Ixo-vec was generally well tolerated. Mild to moderate inflammation was the most common adverse event, which was dose-related and responded to topical corticosteroids
- All participants who received Ixo-vec $2x10^{11}$ vg/eye dose were inflammation free and did not require corticosteroids at the end of the study
- A single IVT injection of Ixo-vec resulted in sustained therapeutic aflibercept expression through at least 3 years. An extension study is ongoing and will follow subjects out to 5 years
- Mean annualized anti-VEGF injections were reduced by 80-98% in all participants, and majority of participants (53%) in $2x10^{11}$ vg/eye dose groups were supplemental injection free over two years
- BCVA and CST were maintained or improved through two years with both doses
- The $2x10^{11}$ dose demonstrated a favorable benefit/risk profile despite short duration corticosteroid prophylaxis, warranting further development for treatment of nAMD

Final 2-Year Analysis

Further Development of Ixo-vec for Wet AMD: The LUNA Study

Lessons Learned and the Path Forward

Inflammation in Ocular Gene Therapy is Correlated with Dose

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Review

Inflammation in Viral Vector-Mediated Ocular Gene Therapy: A Review and Report From a Workshop Hosted by the Foundation Fighting Blindness, 9/2020

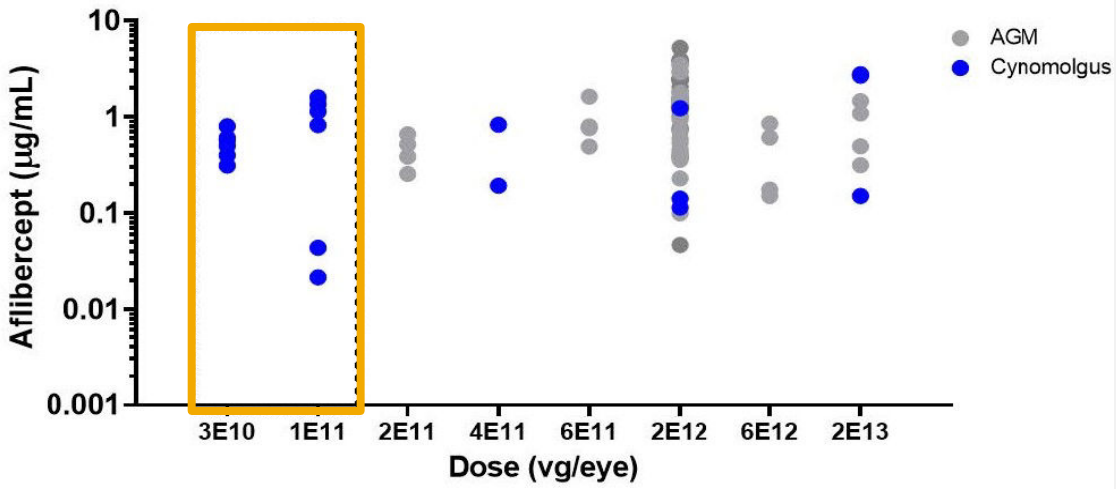
Ying Kai Chan[1], Andrew D. Dick[2,3], Sara Mary Hall[4], Thomas Langmann[5], Curtis L. Scribner[6], and Brian C. Mansfield[7], for the Ocular Gene Therapy Inflammation Working Group

"The workshop's discussions consistently suggested that, in both animals and people, ocular inflammation almost always accompanies gene therapy treatments by any route, and the degree of inflammation is correlated with dose."

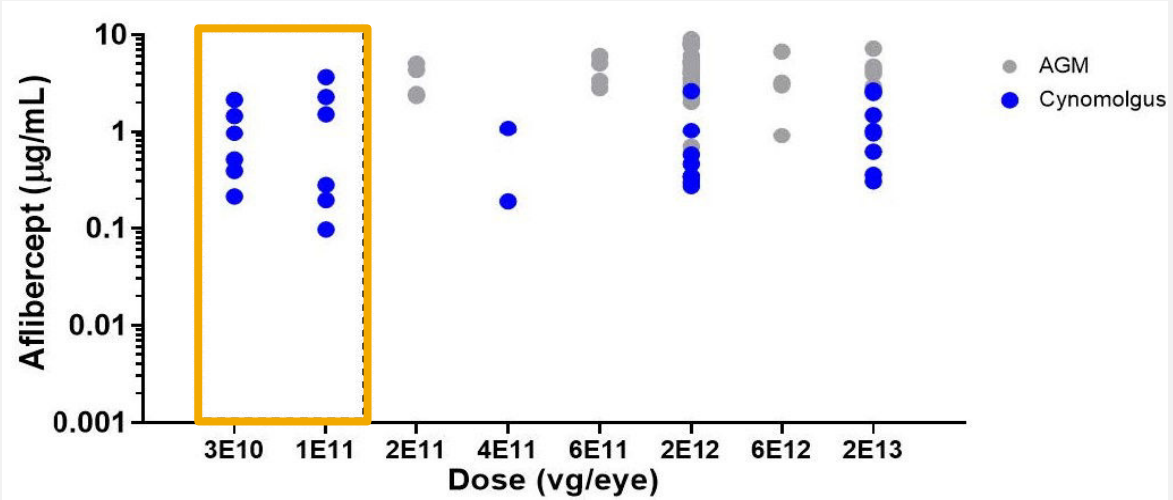
NHP Studies of Ixo-vec Support the Clinical Use of a Lower Dose

Administration of Ixo-vec at doses as low as 3 × 10^{10} vg/eye in NHPs (human equivalent dose* of 6 × 10^{10} vg/eye) are anticipated to provide therapeutic levels of aflibercept in the clinic

Aqueous Humor



Vitreous Humor



Historical data show a near flat dose response over 3 logs. Historical NHP studies conducted in African green monkeys (AGMs, grey) or cynomolgus monkeys (blue). NHPs were administered Ixo-vec at doses of 3 × 10^{10} vg/eye – 2 × 10^{13} vg/eye. Peak aflibercept levels for each NHP in each study were measured via aflibercept ELISA and recorded. Samples from Study ADVM-2110 are outlined with yellow.

*Human equivalent dose is calculated based on a 2-fold difference in vitreous humor volume between NHP/human

Non-Clinical Data Support Efficacy and Tolerability of a Human Equivalent Dose of 6E10 vg/eye of ADVM-022 for the Treatment of Neovascular Age-Related Macular Degeneration. The American Society of Gene and Cell Therapy 2022.
NHP: non-human primate

NHP GLP Study: Ixo-vec Well Tolerated Without Prophylaxis at Clinically Relevant Doses

Summary of Ixo-vec Tolerability

- Minimal inflammation without prophylaxis
- No adverse clinical signs
- Dose-dependent, non-adverse slight to mild inflammation characterized by pigment and cells in the VH
- NOAEL has been determined at $1x10^{11}$ vg/eye (HED $2x10^{11}$ vg/eye)

Ixo-vec Treatment	NHP ID	Day 0	Day 3	Day 8	Day 15	Day 21	Day 25	Day 36	Day 50	Day 64	Day 78	Day 92
Vehicle	1001 OD	0	0	0	0	0	0	0	0	0	0	0
	1001 OS	0	0	0	0	0	0	0	0	0	0	0
	1002 OD	0	0	0	0	0	0	0	0	0	0	0
	1002 OS	0	0	0	0	0	0	0	0	0	0	0
3E+10	2001 OD	0	0	0	0	0	0	0	0	0	0	0
	2001 OS	0	0	0	0	0	0	1	1	0.5	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
	2103 OD	0	0	0	0	0	0	0	0	0	0	0
	2103 OS	0	0	0	0	0	0	0	0	0	0	0
	2004 OD	0	0	0	0	0	0	0	0	0	0	0
	2004 OS	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
	3001 OS	0	0	0	0	0	0	0	0	0	0.5	0.5
	3002 OD	0	0	0	0	0	0	0	0	0	0	0
	3002 OS	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
	3003 OS	0	0	0	0	0	0	2	2	0.5	0.5	0
	3004 OD	0	0	0	0	0	0	2	2	2	1	1
	3004 OS	0	0	0	0	0	1	2	2	2	1	1

Color Codes
4
3
2
1
0.5
0

NHP: non-human primate; NOAEL: no observed adverse effect level; HED: human equivalent dose

Non-Clinical Data Support Efficacy and Tolerability of a Human Equivalent Dose of 6E10 vg/eye of ADVM-022 for the Treatment of Neovascular Age-Related Macular Degeneration. The American Society of Gene and Cell Therapy 2022.

Prophylaxis of Inflammation is Believed to be a Better Strategy than Treatment. The Optimal Regimen Remains to be Determined

tvst

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Inflammation in Viral Vector-Mediated Ocular Gene Therapy: A Review and Report From a Workshop Hosted by the Foundation Fighting Blindness, 9/2020

Ying Kai Chan[1], Andrew D. Dick[2,3], Sara Mary Hall[4], Thomas Langmann[5], Curtis L. Scribner[6], and Brian C. Mansfield[7], for the Ocular Gene Therapy Inflammation Working Group

"Clearly a wide variety of different treatment protocols are being used before, during, and after gene therapy administration to suppress unwanted clinical inflammation, NAbs, or T cell responses. The heterogeneity in research and clinical protocols confounds conclusions about optimal strategies at this time."

Objectives for LUNA Phase 2

Objective I

Determine the Right Dose

- The $2x10^{11}$ vg/eye dose in OPTIC demonstrated robust efficacy and acceptable safety despite suboptimal corticosteroid prophylaxis
- Non-human primate (NHP) studies support efficacy and tolerability of a human equivalent dose of $6x10^{10}$ vg/eye of Ixo-vec

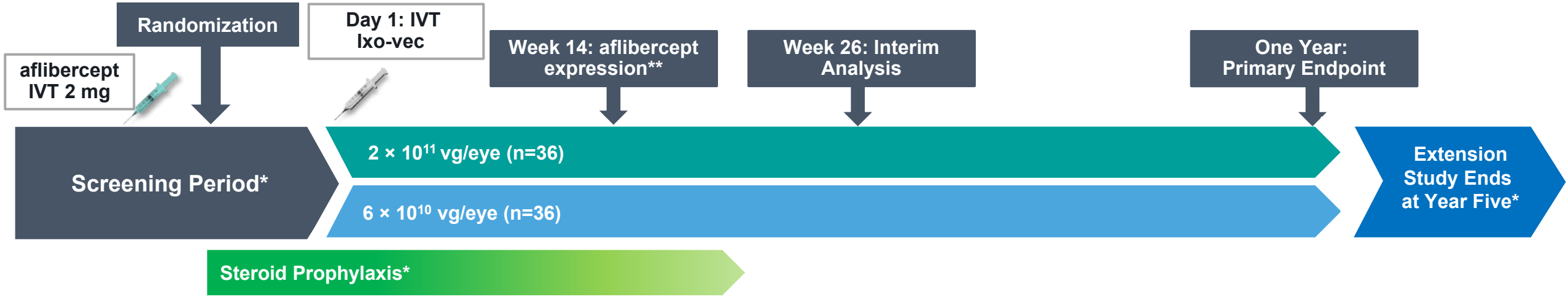
Objective II

Determine the Right Prophylactic Regimen

- Establish a prophylactic regimen that allows efficacy with minimal need for inflammation management post prophylaxis
  - Assess importance of patient adherence to drops
  - Evaluate systemic contribution to immune response
  - Ensure adequate prophylaxis covering the period of peak immune response post IVT gene therapy

LUNA Phase 2 Study in nAMD - Study Design

Objective: The LUNA trial is a multicenter, double-masked, randomized, parallel-group Phase 2 study evaluating a one-time IVT injection of either of two doses of Ixo-vec (ADVM-022), including 2 × 10^{11} vg/eye dose and a new, lower 6 × 10^{10} vg/eye dose in 72 patients



Study Population

- nAMD diagnosis
- 50 years or older
- Demonstrated response to anti-VEGF treatment

Prophylactic Regimens

- **Durezol® topical 22 weeks (n=18)**
- **Ozurdex® IVT (n=18)**
- **Durezol® topical 22 weeks + Prednisone oral 10 weeks (n=18)**
- **Ozurdex® IVT + Prednisone oral 10 weeks (n=18)**

Primary Endpoints

- Mean change in best corrected visual acuity (BCVA) from baseline to one year
- Incidence and severity of adverse events

Secondary Objectives

- Evaluate the effect of Ixo-vec on Best Corrected Visual Acuity (BCVA)
- Assess the durability of a single IVT injection of Ixo-vec
- Evaluate the effect of Ixo-vec on Central Subfield Thickness (CST)
- Assess the effectiveness of prophylactic corticosteroid treatment regimens in minimizing post-prophylactic inflammation

**Study timeline and length of arrows depicted are not to scale*
***Additional levels of aflibercept expression will be measured throughout*