Phase 1/2 Clinical Trial of Intravitreal 4D-150 in Patients with Neovascular (Wet) Age-Related Macular Degeneration: Conference Call

Cohort 1 Interim Safety & Clinical Activity

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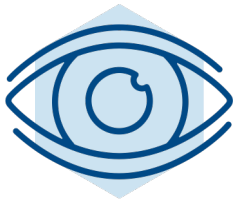
Key Takeaways for 4D-150 Interim Phase 1/2 Clinical Data

DATA CUT-OFF: OCTOBER 13, 2022; COHORT 1 DATA

- **Enrollment Details:**
  - Wet AMD patients requiring **frequent** anti-VEGF injections
  - Phase 1 dose exploration stage enrollment **completed**: 3 cohorts, 15 patients (5 per cohort)
- **Cohort 1 Clinical Data Takeaways:**
  - Safe & well-tolerated: no DLT, no SAE, no significant intraocular inflammation (IOI), no hypotony
  - 3 of 3 patients' aqueous fluid evaluated to date had detectable aflibercept
  - Mean annualized anti-VEGF injection rate in 12 months preceding 4D-150 dosing: **~11**
  - **96.7%** overall reduction in annualized anti-VEGF injection rate
  - **80%** of patients (4 of 5) aflibercept supplemental injection-free (injection-free f/u : 16-40 weeks)
- **Expected Next Steps:**
  - Initiate randomized Phase 2 Expansion (50 patients total; 2 dose levels of 4D-150 vs aflibercept)

4D-150 for Wet AMD & DME

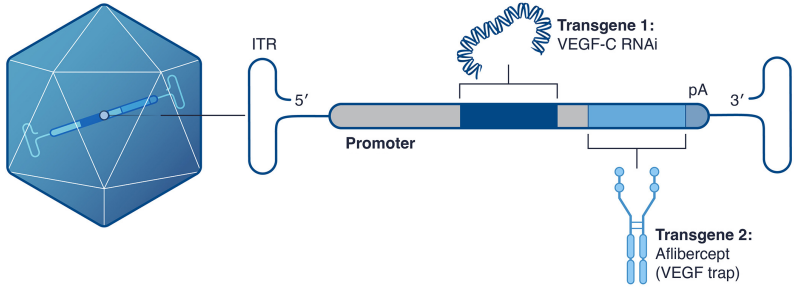


HIGH UNMET MEDICAL NEED

- Frequent Injections
- Patient / Physician Adherence Issues
- Incomplete Responders

EPIDEMIOLOGY: US

- **Wet AMD: ~200,000/year** incidence
- **DME: ~1.2 Million** prevalence
- **$12.3 Billion** 2021 WW branded anti-VEGF sales



PRODUCT DESIGN

- **Vector:** R100
- **Transgene 1:** VEGF-C RNAi
- **Transgene 2:** Aflibercept
- **Promoter:** Ubiquitous

DIFFERENTIATION

- Primate-evolved R100 capsid
- Intravitreal (IVT) routine & safe
- 4 Distinct mechanisms of action

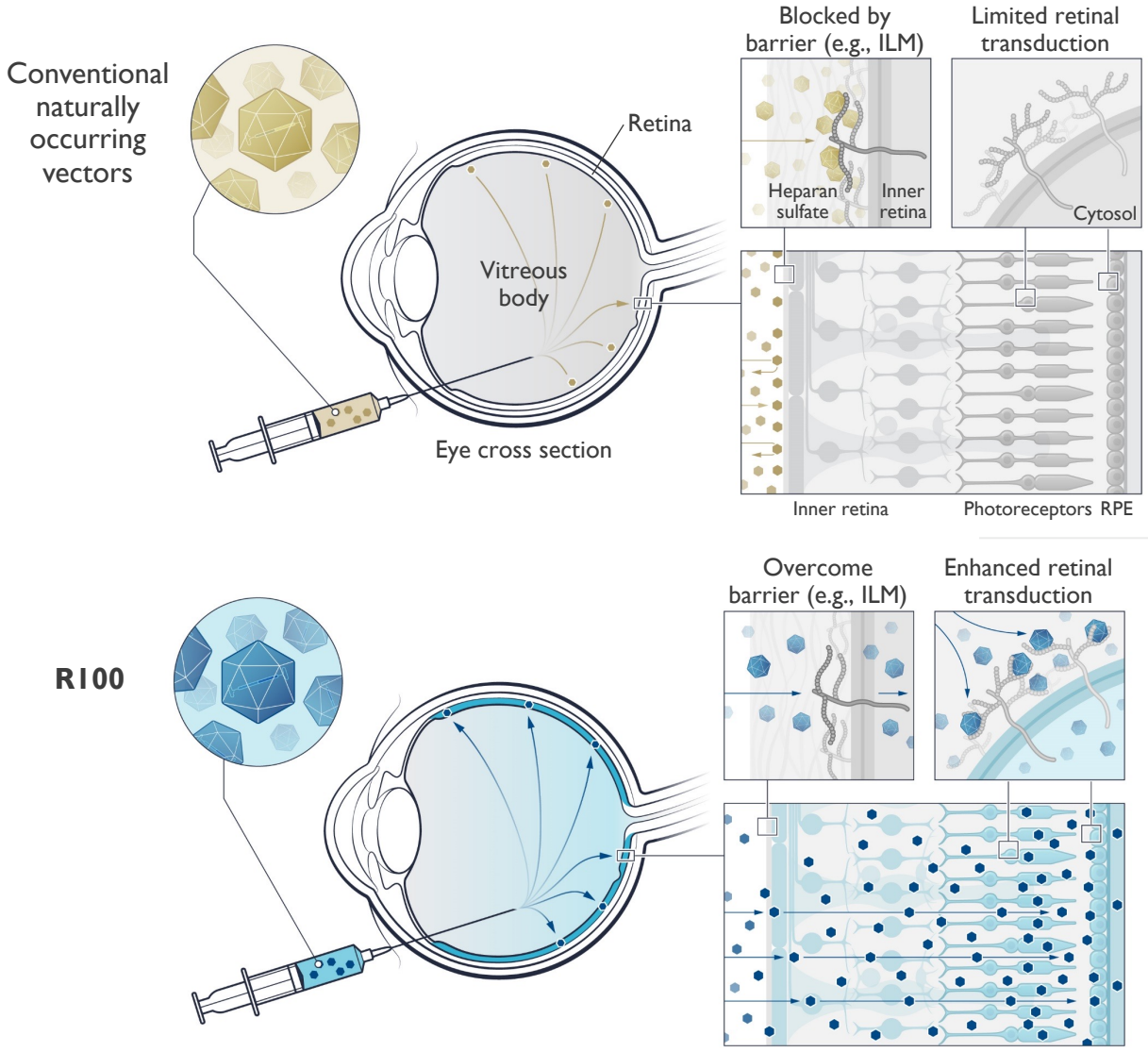
STATUS:

Ongoing Phase 1/2 Clinical Trial

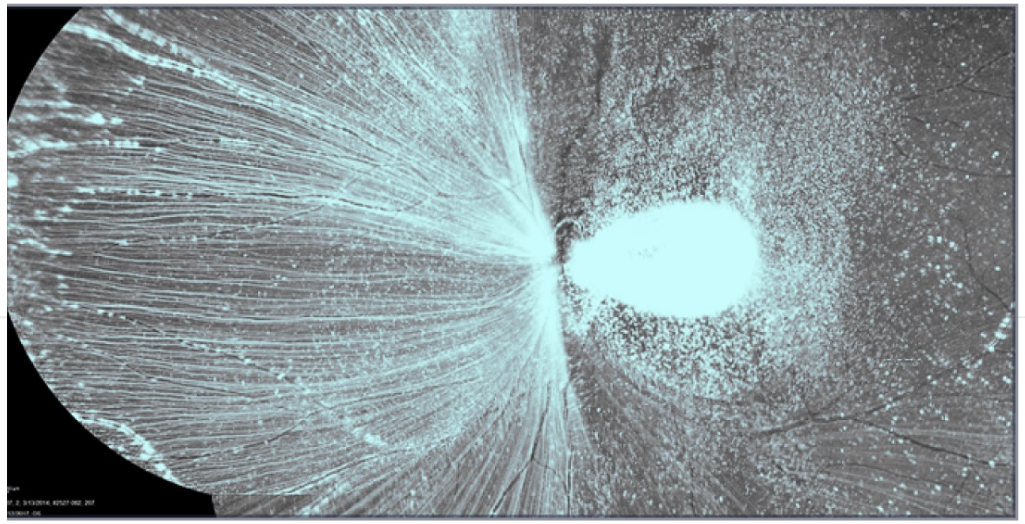
EXPECTED MILESTONE:

Interim Data on all 3 Cohorts Q2-2023

Primate-Evolved R100 Capsid for IVT Delivery of Dual Transgene Payload

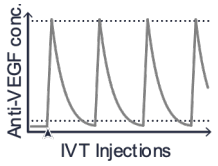
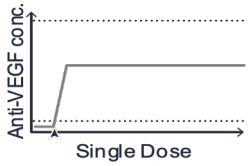
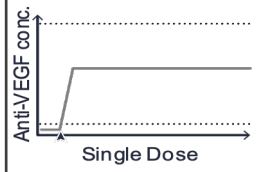
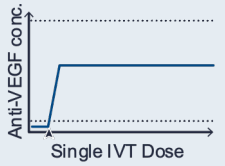


EGFP expression in Primate (NHP):
IVT injection R100.EGFP



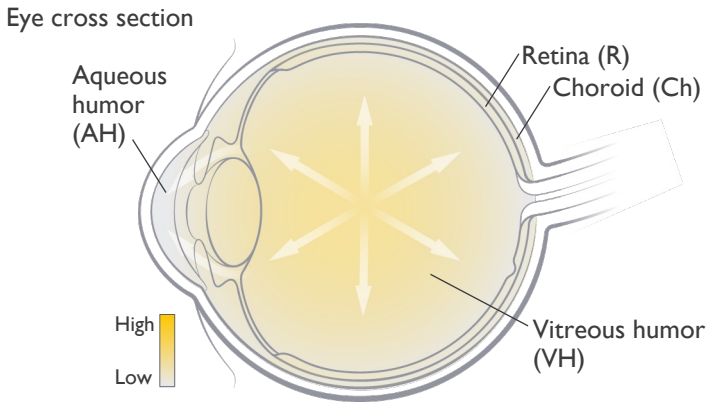
Abbreviations: ILM, inner limiting membrane; RPE, retinal pigment epithelium.

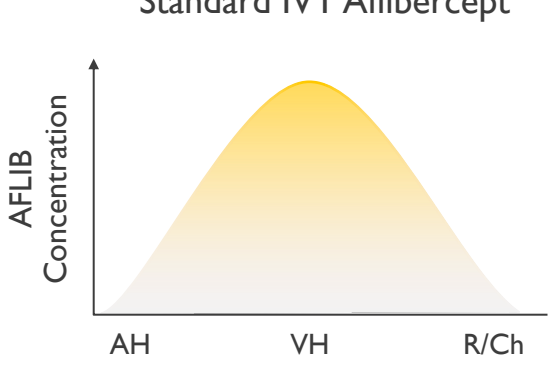
4D-150: Differentiation Versus Other AAV for Wet AMD

MOA	Product Design	Eylea™	RGX-314 (subretinal)	RGX-314 (suprachor)	ADVM-022 (IVT)	**4D-150 (IVT)**
Injection & PK	Pharmacokinetics			Not available		
	Single dose	–	+	+	+	+
	IVT injection	+	–	–	+	+
Anti-VEGF MOA	VEGF A	+	+	+	+	+
	VEGF B	+	–	–	+	+
	PlGF (placental GF)	+	–	–	+	+
	VEGF-C	–	–	–	–	+
Vector & Safety	Primate evolved & optimized	n.a.	–	–	–	+
	No hypotony	+	+	+	–	+
	No chronic uveitis	+	+	+	–	+

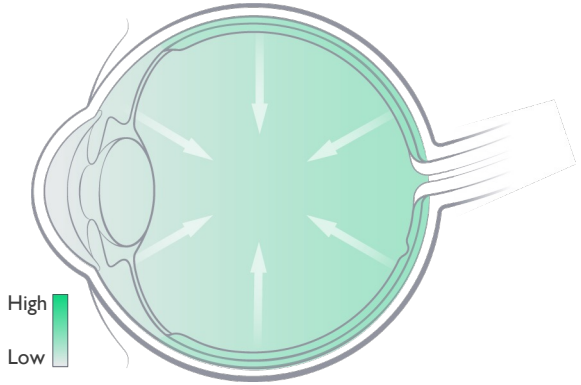
Aflibercept Concentration Gradients Within the Eye: 4D-150 Results in High Level Retina/Choroid Targeting

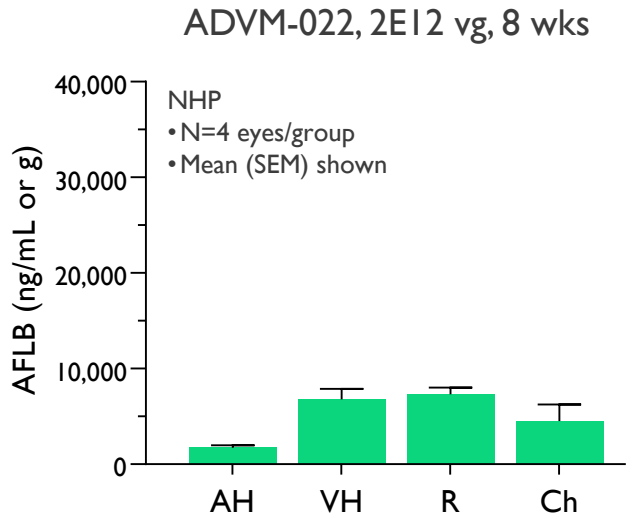
IVT Aflibercept Bolus



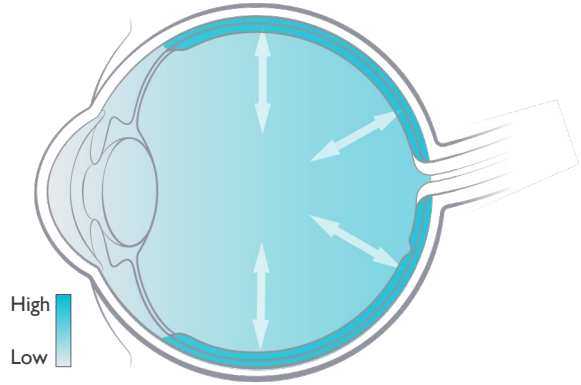


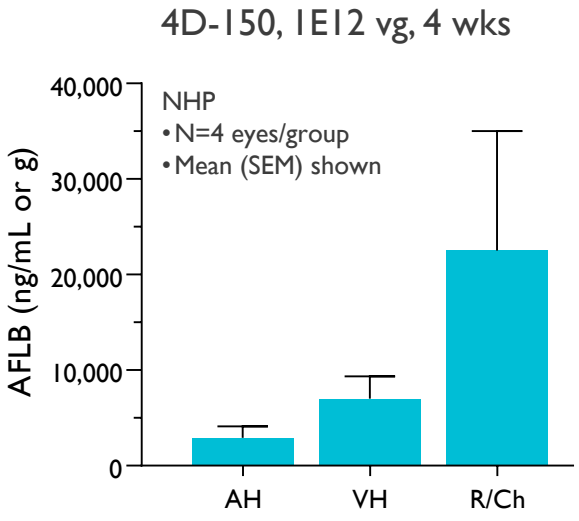
IVT ADVM-022





IVT 4D-150

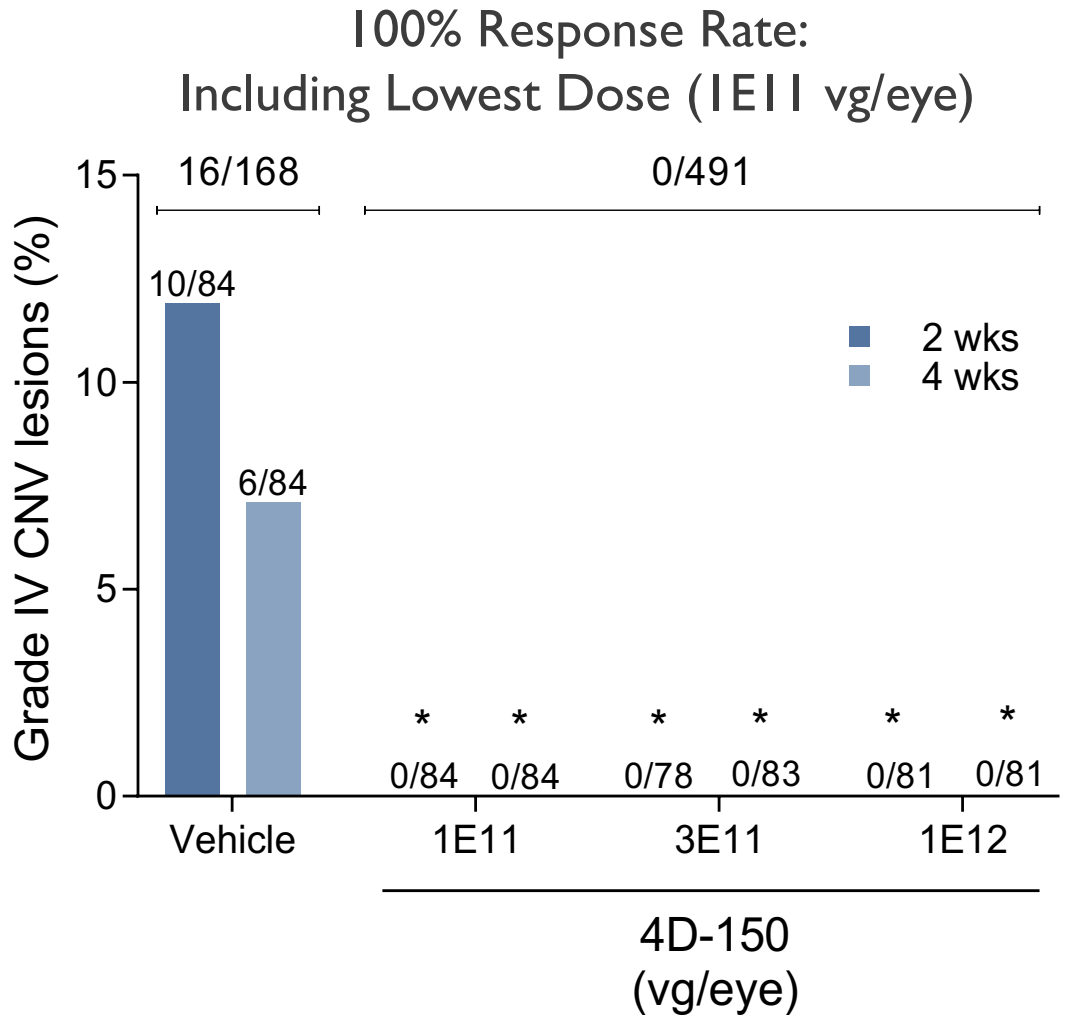




Kiss et al. Mol Therapy 2020;18:345 (Suppl)

4D-150 Efficacy in Primate (NHP) CNV Model:

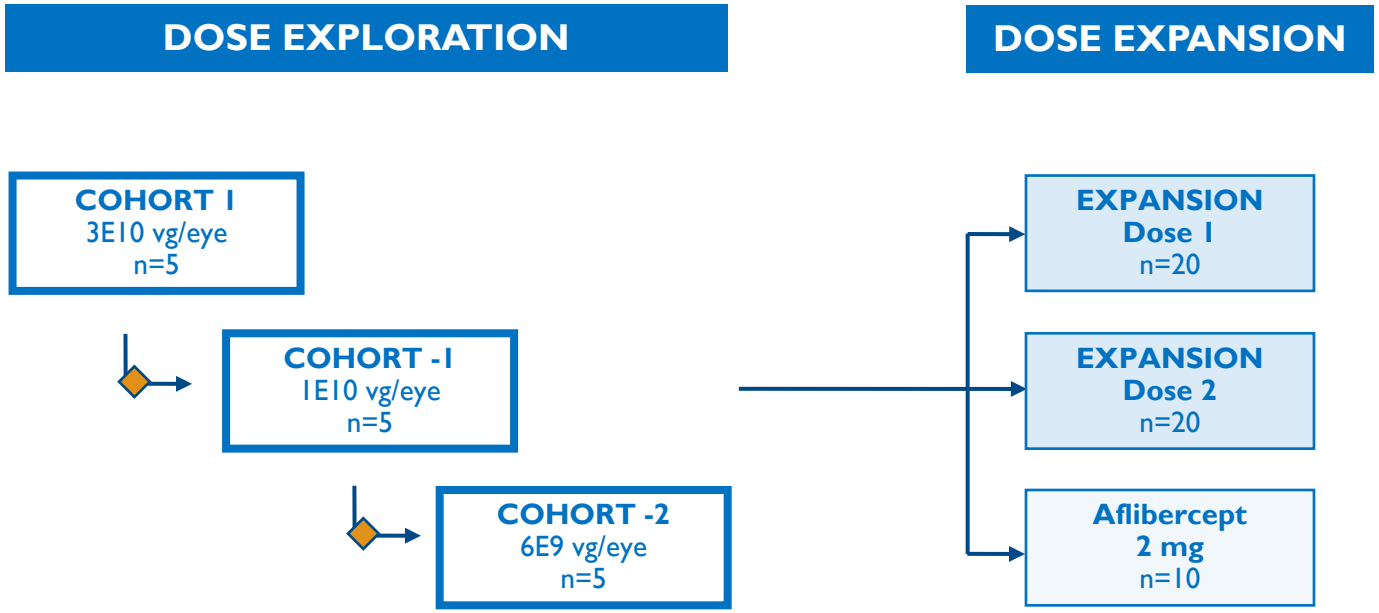
100% SUPPRESSION OF GRADE IV CNV INCLUDING AT LOWEST DOSE OF 1E11 VG/EYE



*p<0.05

4D-150 Phase 1/2 Clinical Trial Design

OPEN-LABEL, PHASE 1/2 TRIAL IN PATIENTS WITH WET AMD RECEIVING ANTI-VEGF TREATMENT



ASSESSMENT SCHEDULE

Topical steroid taper

Visit	Baseline	4D-150	D2	D 14	D 28	W 8-20*	W 24	W 28-48*	W 52	W 56-68*	W 72	W76-100*	W 104
Visit Window (d)	D -7	D 1	–	±2	±2	±7	±7	±2	±7	±7	±7	±7	±7
BCVA	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
SD-OCT	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆

◆ Assessments (OCT assessed by Independent Reading Center). *Study visits completed every 4 weeks.

KEY INCLUSION CRITERIA

- ≥50 yrs old
- CNV secondary to AMD
- ≥25 and ≤78 ETDRS letters: study eye
- Currently receiving anti-VEGF treatment in study eye
- Clinical response to anti-VEGF within prior 12 months

PRIMARY ENDPOINT

- Safety & tolerability

KEY SECONDARY ENDPOINTS

- Percentage of subjects requiring supplemental aflibercept
- Number of required supplemental aflibercept injections
- Aflibercept protein levels in aqueous humor
- Recommended does (n=2) for randomized Phase 2

4D-150 Phase 1/2 Clinical Trial: Cohort Patients 1 (3E10 vg/eye)

BASELINE CHARACTERISTICS & FOLLOW-UP ON TRIAL

Baseline Characteristics	Cohort 1 (3E10 vg/eye dose)				
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (yrs)	75	69	74	89	87
Time since diagnosis (yrs)	3.3	1.5	2.1	6.7	5.9
# anti-VEGF injections (12 months prior to 4D-150 IVT injection)*	12	6	11	13	13
~# of months follow-up post-4D-150 IVT injection	10	9	8	4	3

*includes protocol specified aflibercept injection at Day -7

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4D-150 Phase 1/2 Clinical Trial: Cohort 1 Safety Summary

DATA TO DATE DEMONSTRATED 4D-150 AT THIS DOSE WAS SAFE & WELL-TOLERATED

- No SAE
- No DLT
- No clinically significant 4D-150-related adverse events
- No clinically significant intraocular inflammation, no endophthalmitis, no retinal vasculitis, no choroidal effusions, no retinal artery occlusion
- No hypotony

As of 07OCT2022.

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4D-150 Phase 1/2 Clinical Trial: Ocular Examinations Background

BACKGROUND & DIFFERENTIATION

- Prior AAV candidates associated with:
  - Significant intraocular inflammation: inflammatory cells, haze, flare
  - Pigment changes
- 4D-150 vector differentiation:
  - R100 primate-evolved vector targeted to retina
- 4D-150 cohort 1 dose differentiation:
  - Low dose: Other AAV candidates have treated with 7- to 30-fold higher doses
- Methods:
  - Aqueous humor & vitreous humor; inflammatory and pigmented cells; flare & haze
  - Wk 2 & 4, then every 4 weeks

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Ophthalmic Exam: Aqueous Cell & Flare Analyses
2+ Pigmented Cells at a Single Timepoint (1 of 39) – No WBC or Flare

		SCR	D14	D28	W8	W12	W16	W20	W24	W28	W32	W36	W40
Patient 1	AC Cell	0	0	0	0	0 / 2 pc	0*	0	0	0	0*	0*	0
	AC Flare	0	0	0	0	0	0	0	0	0	0	0	0
Patient 2	AC Cell	0	0	0	0	0	0	0	0	0	0	0	
	AC Flare	0	0	0	0	0	0	0	0	0	0	0	
Patient 3	AC Cell	0	0	0	0	0	0	0	0	0	0		
	AC Flare	0	0	0	0	0	0	0	0	0	0		
Patient 4	AC Cell	0	0	0	0	0	0						
	AC Flare	0	0	0	0	0	0						
Patient 5	AC Cell	0	0	0	0	0							
	AC Flare	0	0	0	0	0							

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AC=anterior chamber, pc=pigmented cells;

* trace pigmented cells

Ophthalmic Exam: Vitreous Cell & Haze Analyses
Trace Mixed Cells at a Single Timepoint (1 of 39) – No WBC or Haze

		SCR	D14	D28	W8	W12	W16	W20	W24	W28	W32	W36	W40
Patient 1	VC	0	0	0	0	0	0	0	0	0	0	0	0
	VH	0	0	0	0	0	0	0	0	0	0	0	0
Patient 2	VC	0	0	0	0	0	0	0	0	0	0	0	
	VH	0	0	0	0	0	0	0	0	0	0	0	
Patient 3	VC	0	0	0	0	0.5[1]	0	0	0	0	0		
	VH	0	0	0	0	0	0	0	0	0	0		
Patient 4	VC	0	0	0	0	0	0						
	VH	0	0	0	0	0	0						
Patient 5	VC	0	0	0	0	0							
	VH	0	0	0	0	0							

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VC=vitreous cell, VH=vitreous haze, PC=pigmented cells;)

[1]Reported as "mixed pigmented & nonpigmented"

Aflibercept Concentrations in Aqueous Humor Cohort 1: Week 12

AFLIBERCEPT DEMONSTRATED IN ALL 3 PATIENTS' AQUEOUS HUMORS EVALUATED TO DATE

- Aqueous Humor (AH) collected Week 12
- Retinal concentrations predicted to be higher than AH
- 3 patients' aqueous humor samples evaluated to-date
- **All 3 patients had aflibercept concentrations within expected therapeutic range**
- Aflibercept data on 3 dose exploration cohorts (n=15) to be reported at a future medical meeting

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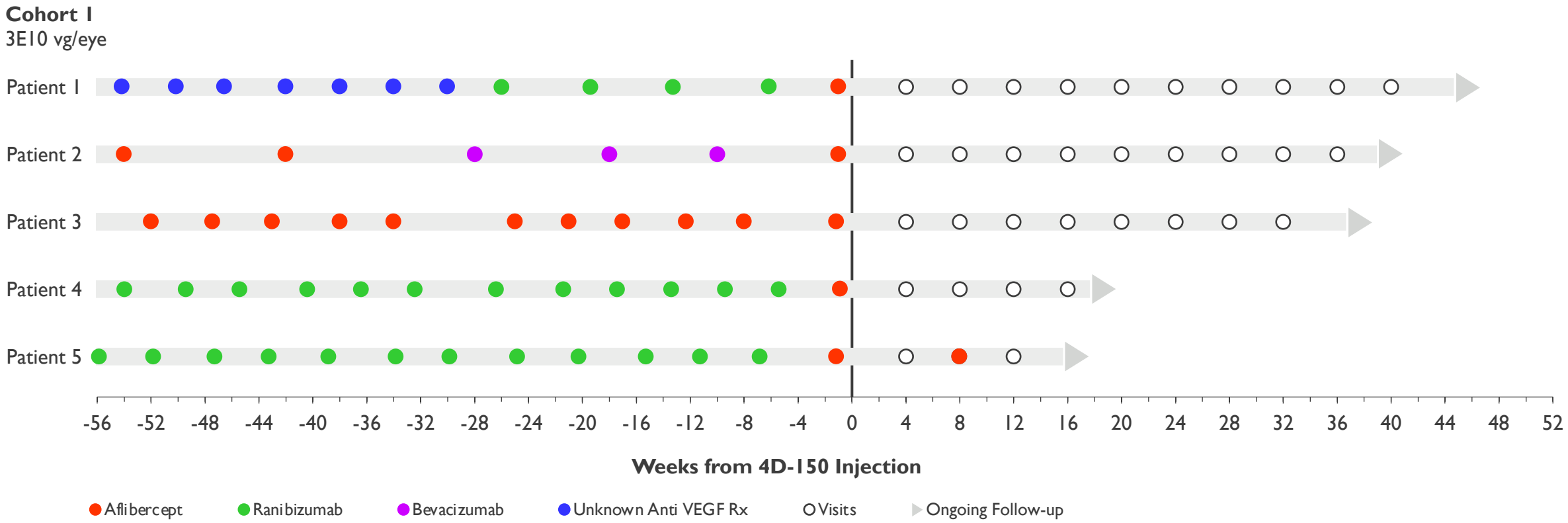
Efficacy Data Cohort 1: 96.7% Reduction in Anti-VEGF Injection Rate

80% OF PATIENTS INJECTION FREE; INJECTION FREE FOLLOW UP 16-40 WEEKS

- **96.7% reduction** in annualized anti-VEGF injection rate
- **80% anti-VEGF injection free**



4D-150 Clinical Data Summary, Implications & Next Steps

CLINICAL PROOF-OF-CONCEPT FOR TOLERABILITY, AFLIBERCEPT EXPRESSION & ANTI-VEGF EFFICACY

- **Clinical Data Summary:**
  - **Safe & well-tolerated**: No clin significant AEs, no clinically significant IOI, no hypotony
  - **96.7% overall reduction** in annualized anti-VEGF injection rate
  - **80% of patients (4 of 5) aflibercept injection-free** (injection-free f/u : 16-40 weeks)
- **Implications:**
  - 4D-150 clinical proof-of-concept
  - R100 vector clinical proof-of-concept
  - Platform validation: Therapeutic Vector Evolution
- **Expected Next Steps:**
  - Report clinical data on all 3 Phase 1 cohorts: Q2 2023
  - Initiate randomized Phase 2 Expansion (50 patients total; 2 dose levels vs aflibercept): Q1 2023
  - Large market ophthalmology pipeline expansion

THANK YOU