Bilateral Ixoberogene Soroparvovec (Ixo-vec) NHP Tolerability and Efficacy Following a Staggered Dosing Interval between Eyes - Gene Therapy nAMD

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Disclosures

Full time employee and shareholder of
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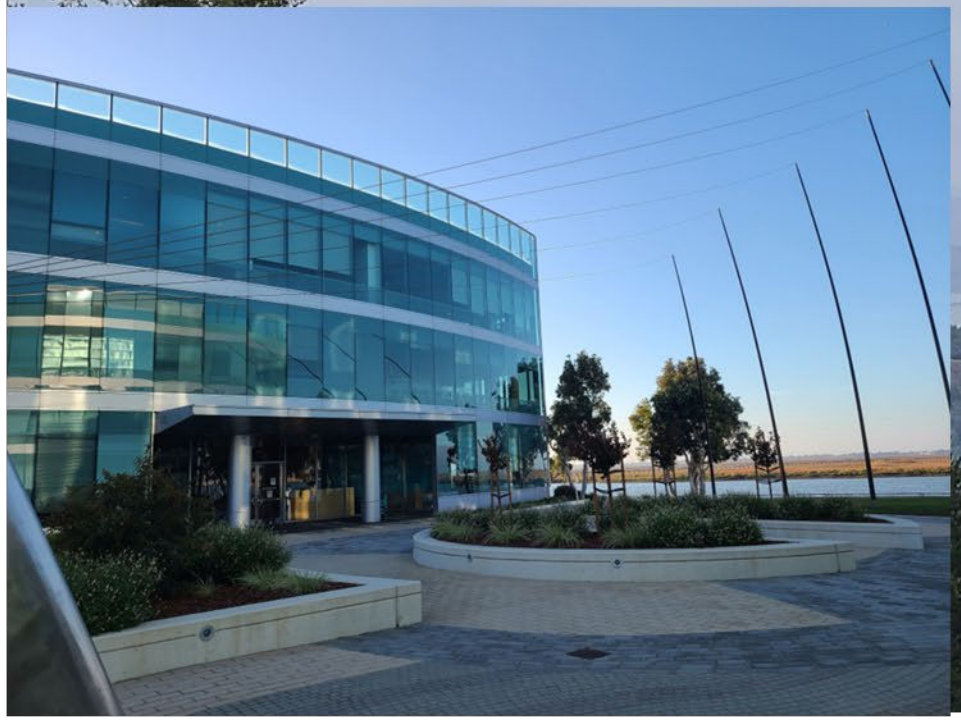

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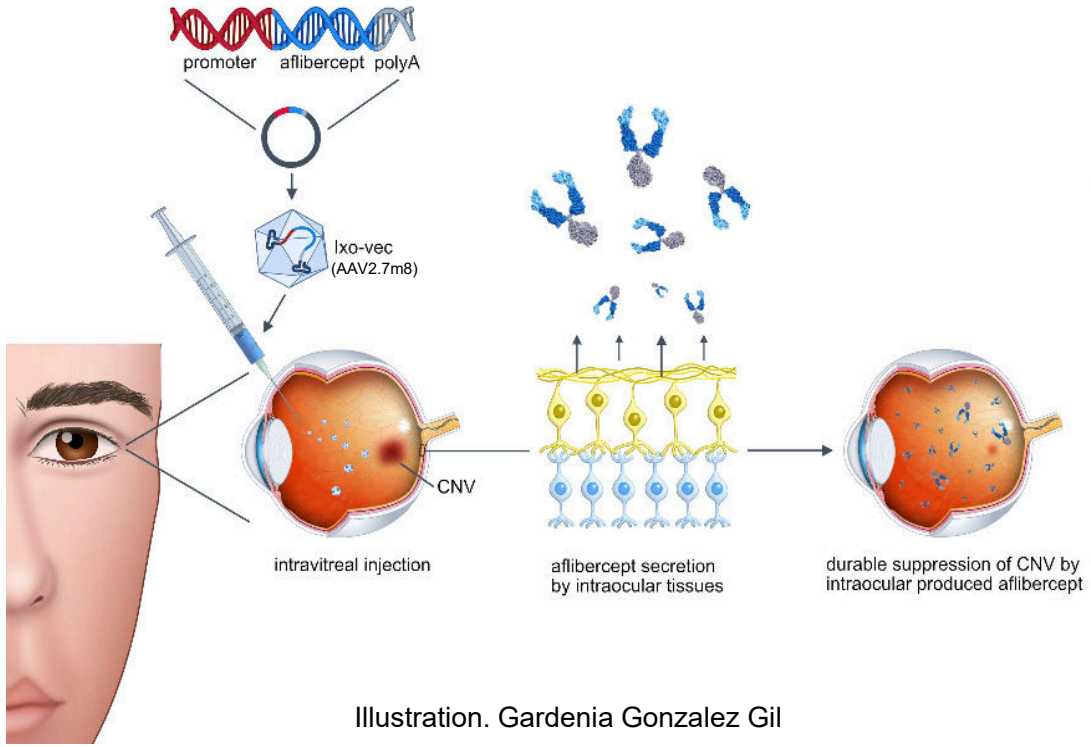
Ixo-vec is a gene therapy biofactory approach designed for continuous delivery of aflibercept (anti-VEGF) by single intravitreal injection

- Bolus intravitreal (IVT) anti-VEGF agents are the standard of care for neovascular age-related macular degeneration (nAMD)
- Frequent monitoring and injections impose a significant burden on patients, caregivers, and physicians
- Fluctuations of anti-VEGF levels linked to bolus anti-VEGF leads to fluctuations in retinal fluid and to long term vision loss



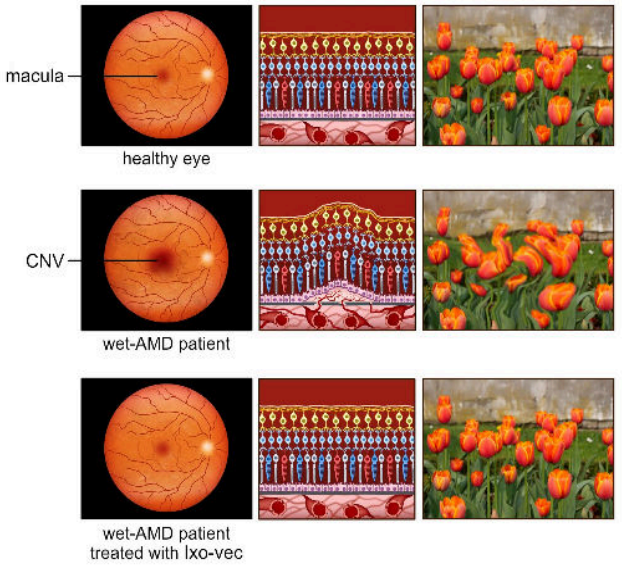


Illustration. Gardenia Gonzalez Gil

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Asynchronous bilateral development of nAMD necessitates investigation of staggered dosing of Ixo-vec

Neovascular AMD is bilateral in 42% of patients

- ~10% bilateral conversion per year
- Many patients will have one eye initially administered with Ixo-vec
- Fellow eye may need to be treated after several months to years

Potential for immune system sensitization after first eye administration include:

- Risk of increased immune response after fellow eye dosed
- Loss of efficacy due to formation of neutralizing antibodies or anti-drug antibodies

Today's Focus

- Two non-human primate (NHP) studies evaluating bilateral, staggered administration of Ixo-vec with a 2-month dosing interval between eyes
  - Staggered dosing of the second eye is well tolerated with potential for clinically meaningful aflibercept levels in both eyes
  - Ocular humoral response is compartmentalized to the dosed eye
- NHP single eye administration study of Ixo-vec
  - Confirmed humoral response observations from bilateral, staggered studies

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Two studies to examine feasibility of Ixo-vec staggered administration to fellow eyes:
Second eye administration of high doses of Ixo-vec two months after first eye administration

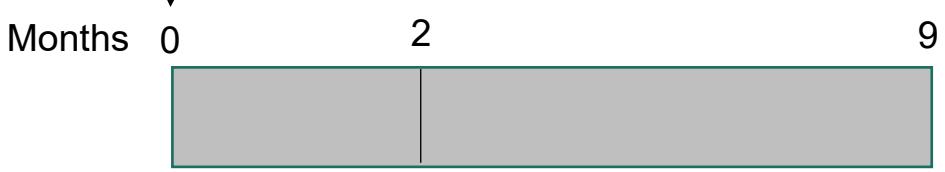
2E12 Study

Ixo-vec

- 2-month interval between doses
- **2E12 vg/eye***
- No immunosuppression
- 9-month monitoring

IVT injection of test article OD **(first eye)**

IVT injection of test article OS **(second eye)**



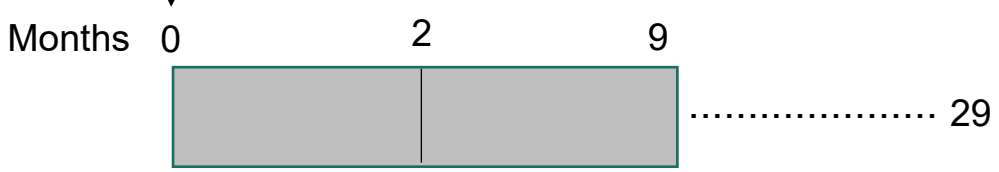
6E11 Study

Ixo-vec

- 2-month interval between doses
- **6E11 vg/eye***
- No immunosuppression
- 29-month monitoring

IVT injection of test article OD **(first eye)**

IVT injection of test article OS **(second eye)**



Assessments

- **Tolerability**-Ophthalmic exams, ocular histopathology
- **Humoral response-** Systemic and ocular neutralizing antibodies (NAbs) and total antibodies (Tabs)
- **Aflibercept levels-** Vitreous collections (ELISA)

*** HED 4E12 and 1E12 vg/eye**

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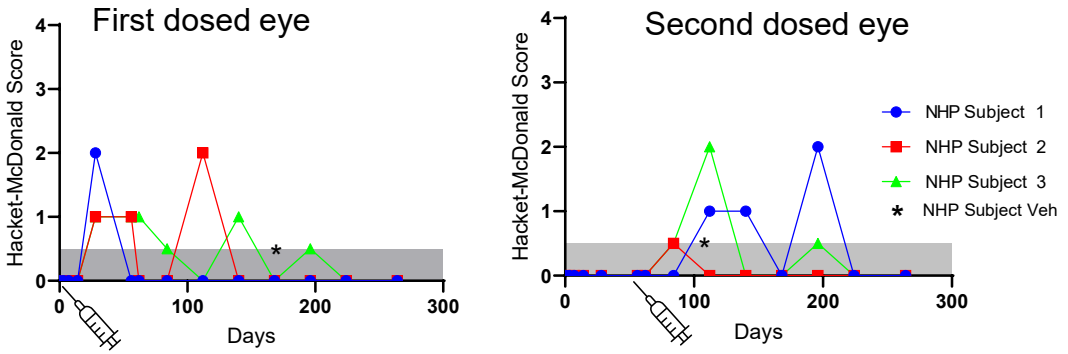
Bilateral, staggered administration does not exacerbate fellow eye IOI and results in similar therapeutic range levels of aflibercept in both eyes

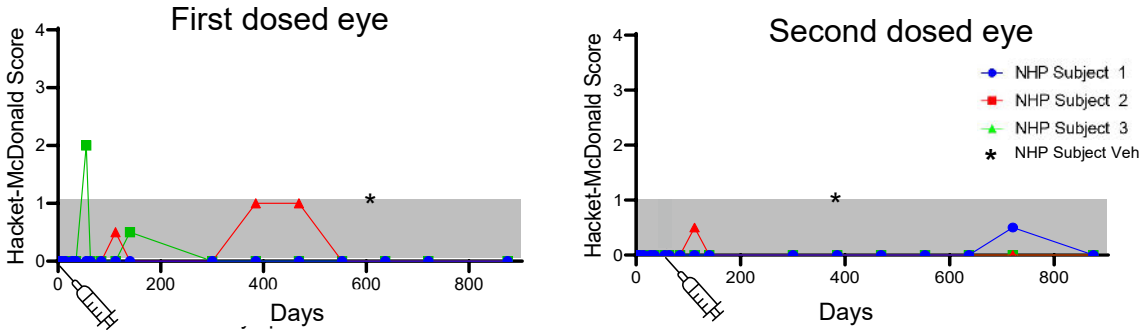
Bilateral, Staggered Administration Tolerability

No increased inflammation in staggered dosed eyes in comparison with concurrent dosing observed

Ophthalmic scores (vitreous cells, Dose 2E12 vg/eye*)



Ophthalmic scores (vitreous cells, Dose 6E11 vg/eye*)

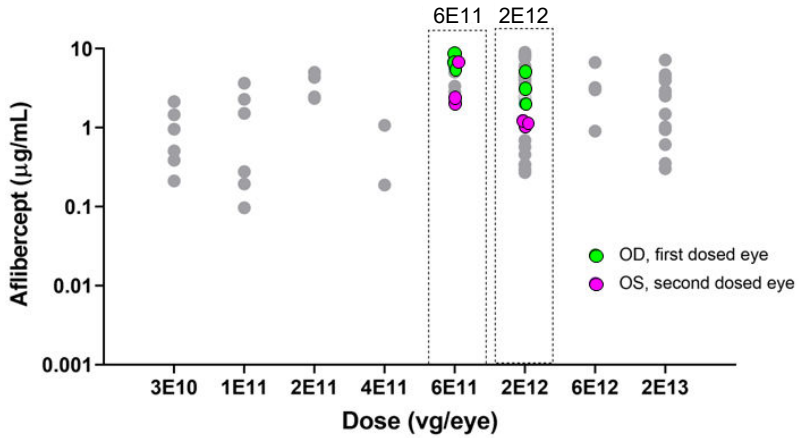


Microscopic findings- Limited to mononuclear cell infiltrates of minimal severity

Ocular levels of aflibercept

Staggered dosing resulted in similar aflibercept production in both eyes

- Peak aflibercept levels in both eyes were within range measured across multitude of nonclinical studies in animals across 3 logs of Ixo-vec doses



- Aflibercept levels in the second eye trended lower

  Potential explanations under investigation

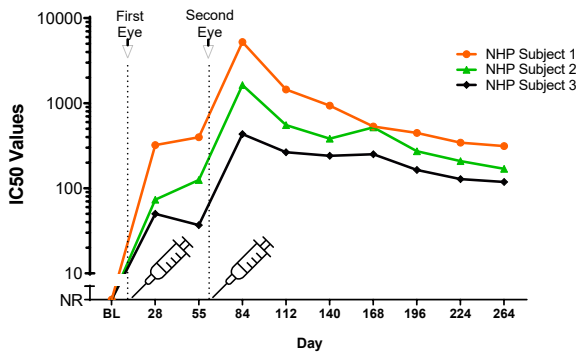
*** HED 4E12 and 1E12 vg/eye**

Nonclinical data support feasibility of Ixo-vec staggered dosing to fellow eyes:
Ocular Ab levels suggest compartmentalized humoral immune response in the dosed eye

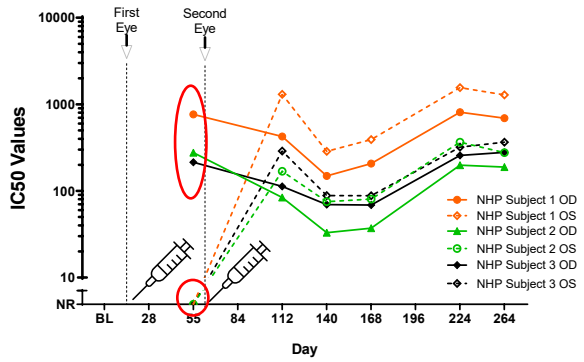
2E12* Study

Nabs (IC50 assay)

Serum

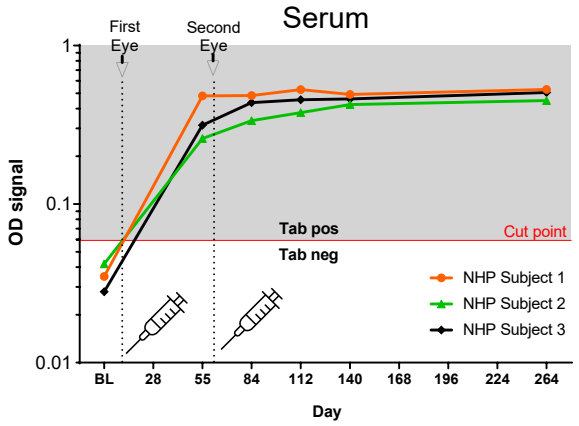


Vitreous

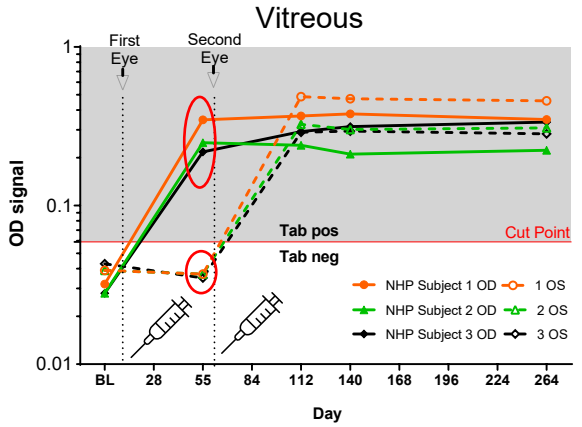


Tabs (Cut point assay)

Serum



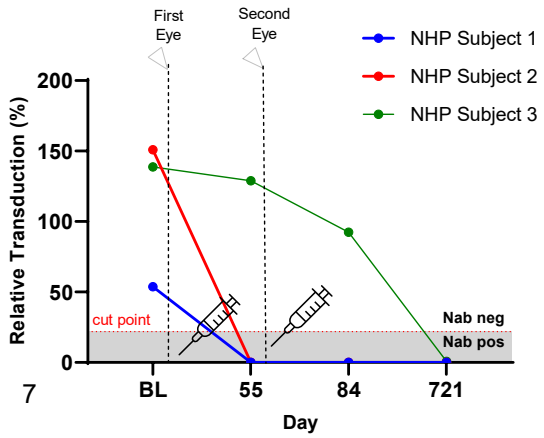
Vitreous



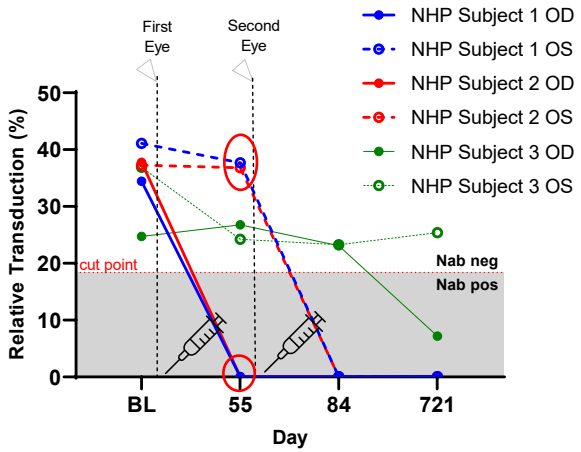
6E11* Study

Nabs (Cut point assay)

Serum



Vitreous

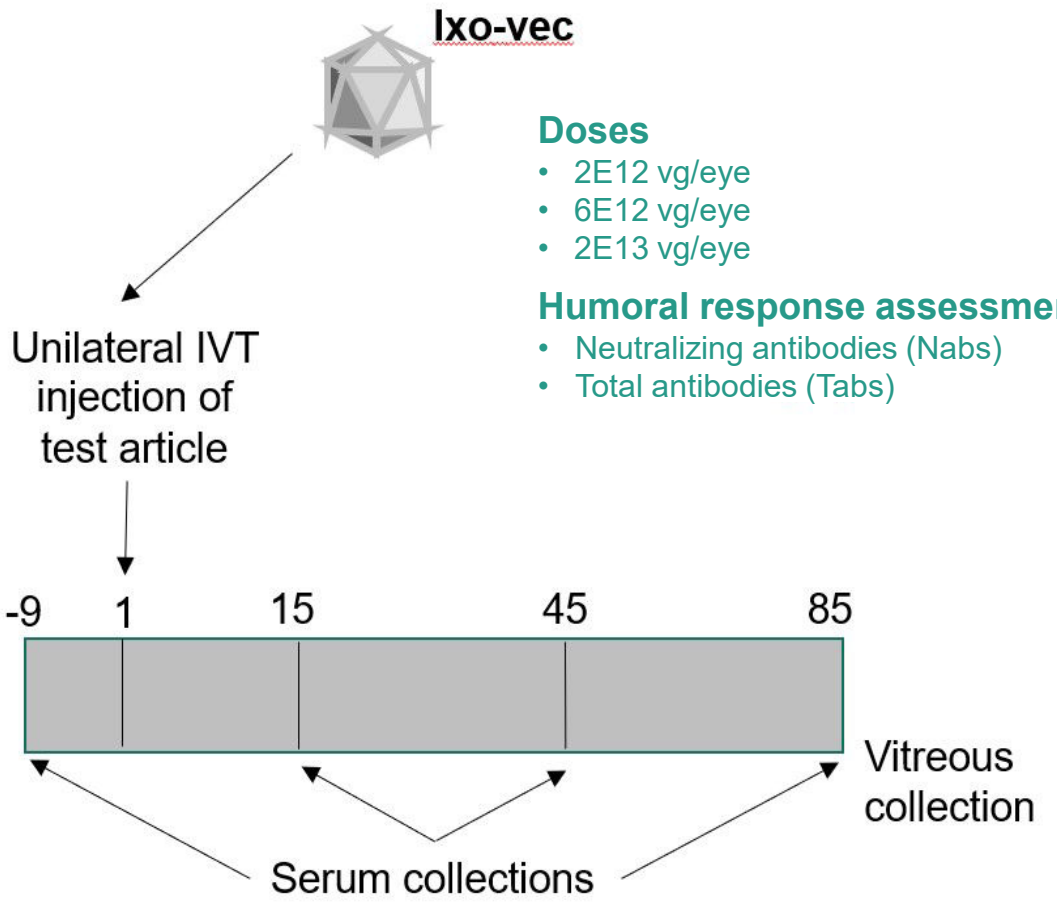


- **First Injection-** Humoral response (Nabs, Tabs) in serum and first eye
- **Second Injection-** Humoral response in second eye

Despite serum Nab and Tab, no antibodies detected in second eye prior to administration.

*** HED 4E12 and 1E12 vg/eye**

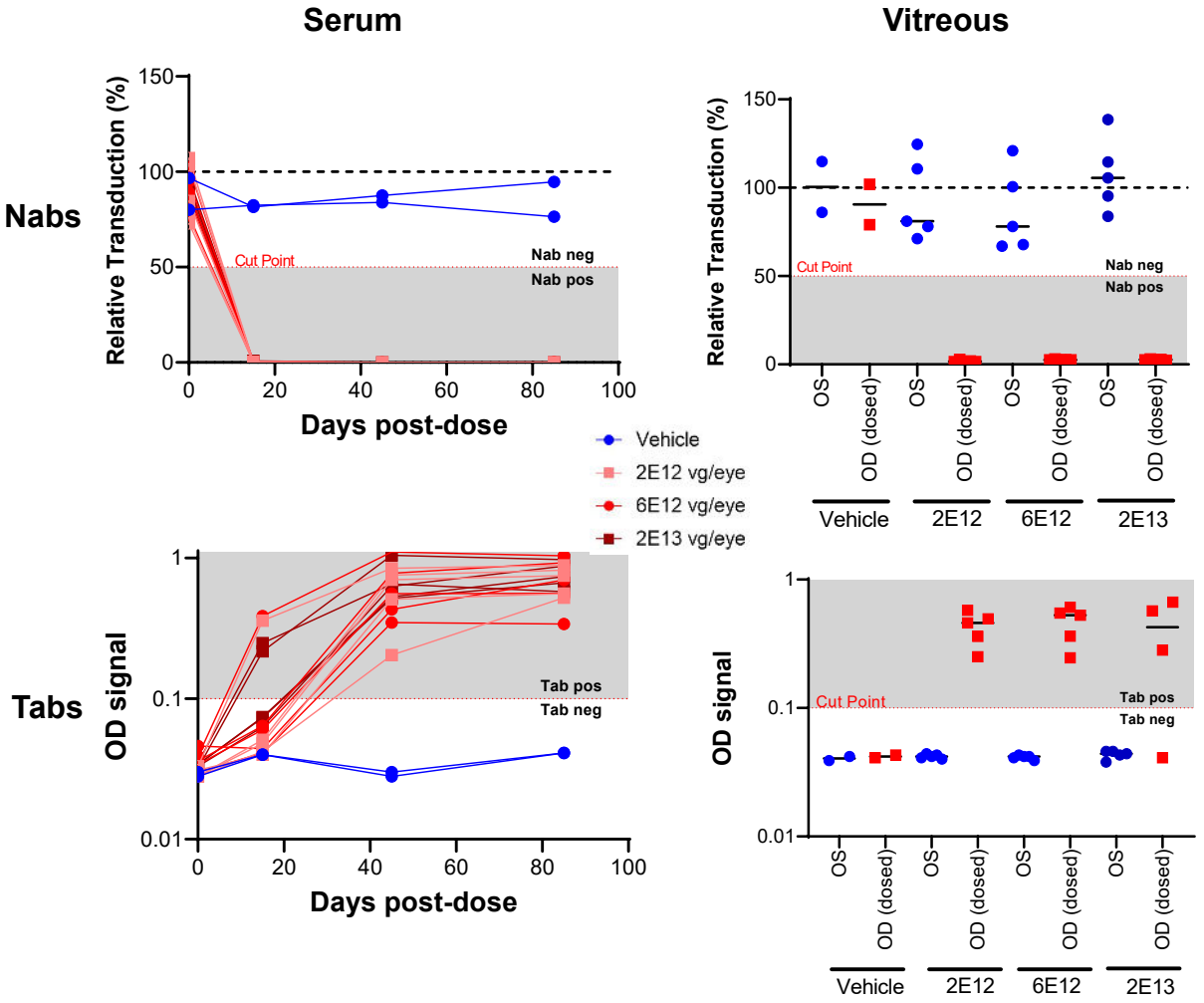
Single eye administration confirms humoral response in serum and administered eye but not naïve eye



Doses
- 2E12 vg/eye
- 6E12 vg/eye
- 2E13 vg/eye

Humoral response assessment
- Neutralizing antibodies (Nabs)
- Total antibodies (Tabs)

Despite a systemic humoral response (Nabs, Tabs) after single eye administration, fellow eye remained negative



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Conclusions

Ixo-vec, a potential single administration treatment for nAMD, is well tolerated with second eye administration

- **NHP data suggests feasibility of Ixo-vec bilateral, staggered administration**
  - No exacerbated inflammation associated with staggered administration
  - Peak aflibercept levels were within therapeutic range in both eyes with bilateral, staggered administration
- **This data demonstrates for the first time that the ocular humoral response in NHP is compartmentalized to the eye dosed with AAV capsid**
  - Despite elevated systemic humoral response after first eye injection, second eye antibodies were undetectable prior to injection
- **Clinical translation of the findings around systemic/ocular humoral response will need to be evaluated in the clinical disease setting of nAMD**

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