Ixoberogene soroparvovec (Ixo-vec) for the treatment of neovascular age-related macular degeneration: Nonclinical data in support of human equivalent dose of 6E10 vg/eye and staggered bilateral dosing

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ADVERUM

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

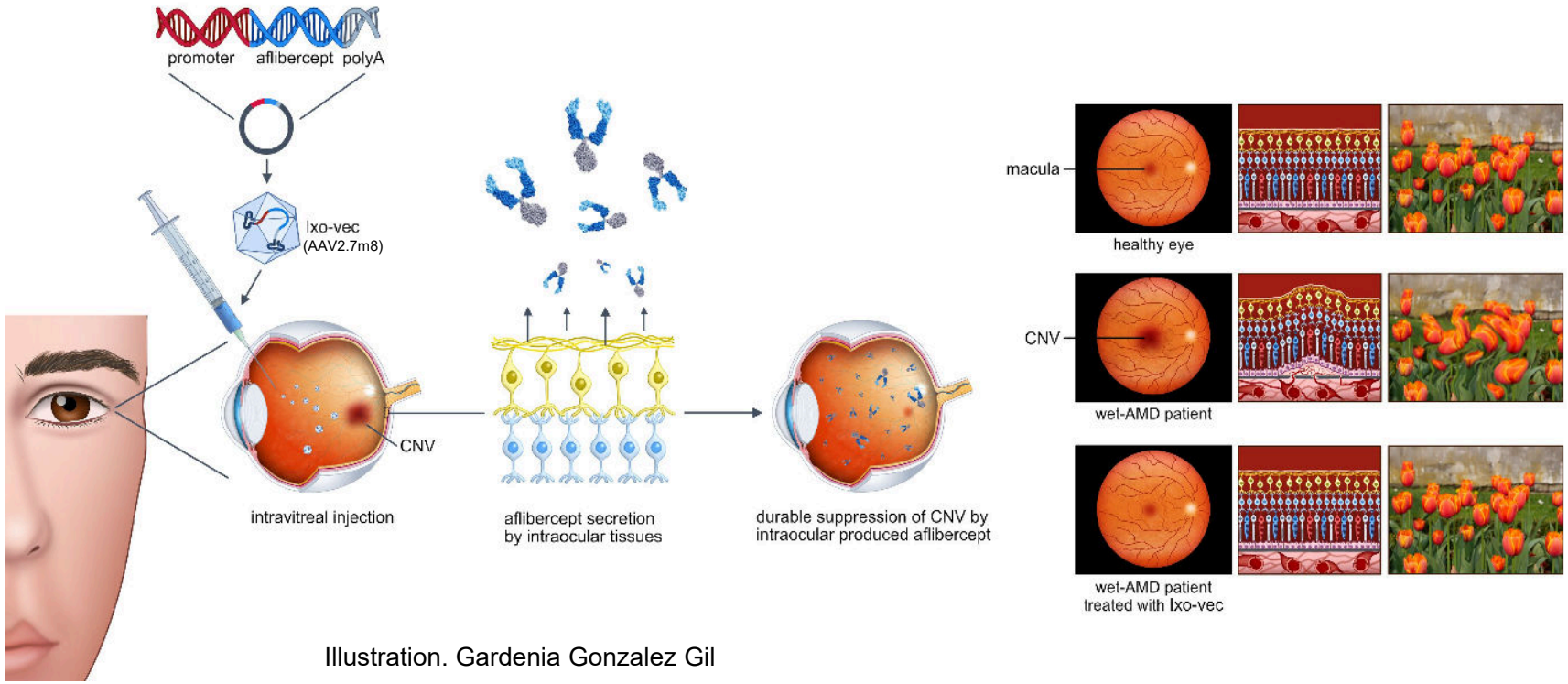

Illustration. Gardenia Gonzalez Gil

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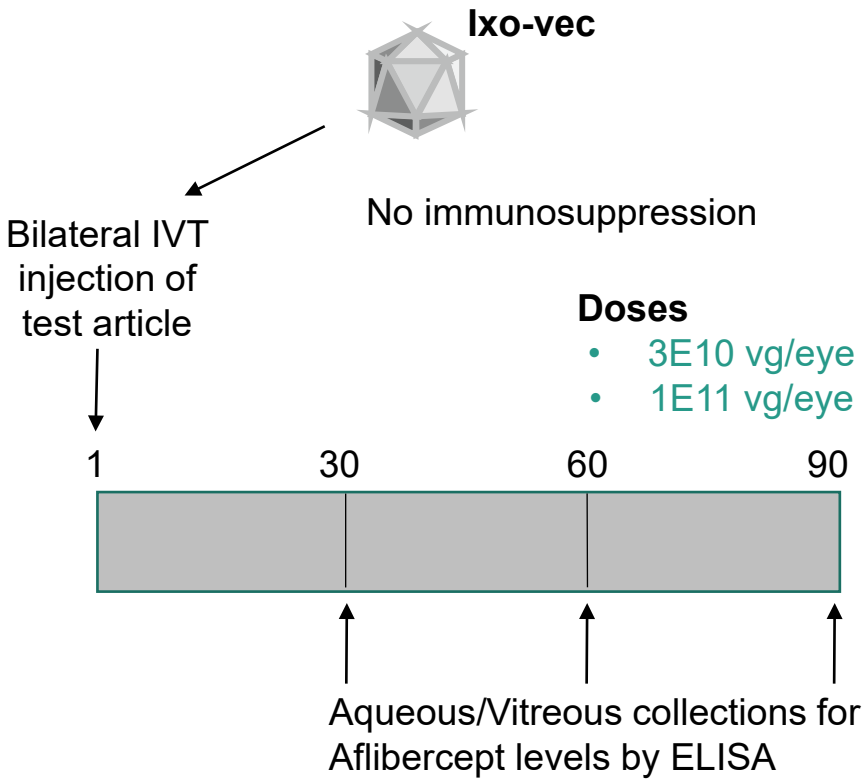
Today's Focus

1. **Tolerability and ocular levels of aflibercept with lower dose of Ixo-vec**
   - GLP-tox study: NHP administered doses of 1E11 or 3E10 vg/eye (HED, 2E11 or 6E10 vg/eye)
   - Both doses were well tolerated with production of clinically meaningful aflibercept levels

2. **Feasibility of staggered dosing of the fellow eye in nAMD patients**
   - Two NHP Studies evaluating staggered bilateral administration of Ixo-vec with a 2-month dosing interval between eyes
   - Results suggested staggered dosing of the second eye is well tolerated with potential for clinically meaningful aflibercept levels in both eyes

Nonhuman primate study established that lower doses of Ixo-vec are well tolerated

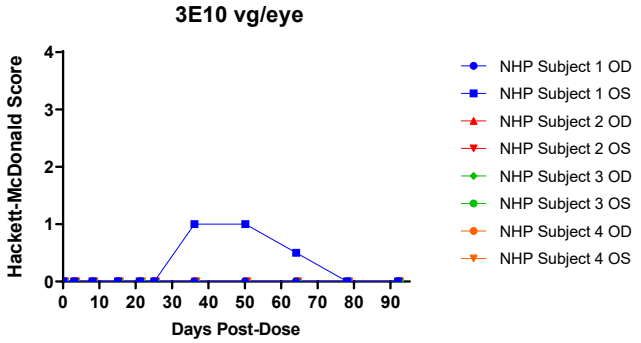
GLP-Tox Study

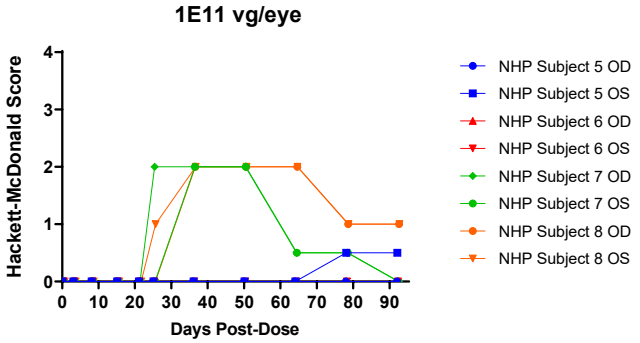


Ocular Safety Assessments
- Ophthalmic exams
- Tonometry (intraocular pressure)
- Optical Coherence Tomography (OCT)
- Electroretinography (ERG)

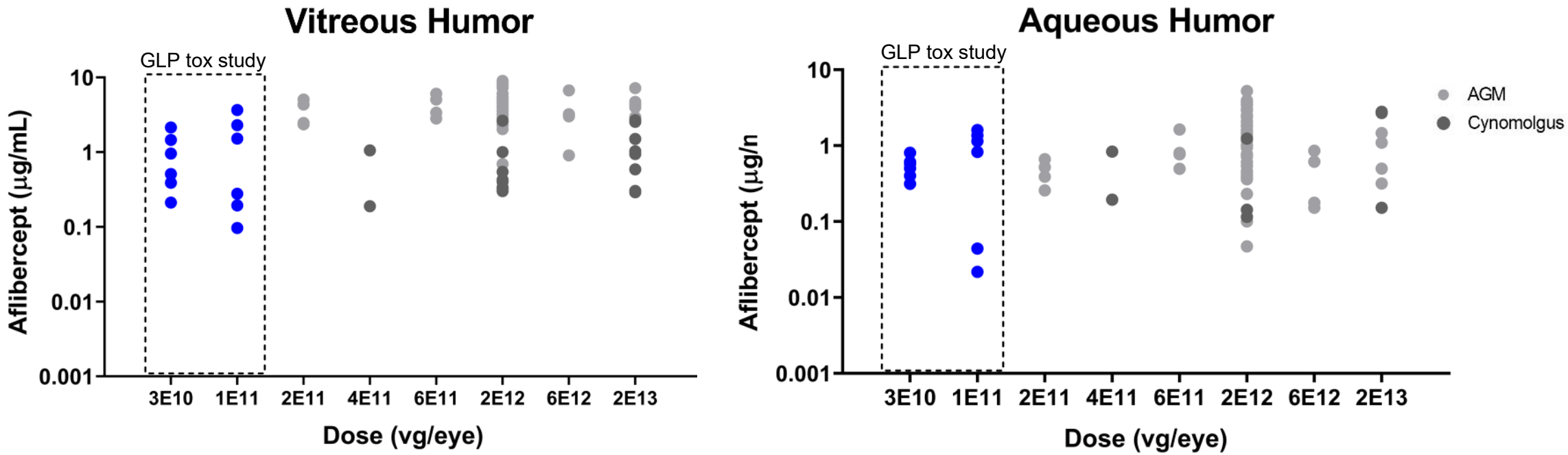
- No adverse systemic clinical signs observed
- Observations limited to non-adverse slight to mild dose dependent ocular inflammation characterized by pigment and vitreous cells
- No abnormalities in the anterior segment or lens
- IOP within normal range
- Microscopic findings: minimal mononuclear cell infiltrates of minor severity considered non-adverse
- **No Observed Adverse Effect Level (NOAEL) identified at 1E11 vg/eye**

Ophthalmic scores (vitreous cells)





Well tolerated doses of Ixo-vec in NHP result in clinically meaningful levels of ocular aflibercept



- Peak Aflibercept levels consistent with historical NHP data of non-dose proportional response over nearly 3 logs
- Well-tolerated doses in the study express aflibercept at levels comparable to those observed in human trial (Phase 1, OPTIC, 2E11 or 6E11 vg/eye)
- Data suggest efficacy of low dose 6E10 vg/eye (HED of 3E10 vg/eye NHP dose) evaluated in ongoing Phase 2 (LUNA) trial

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

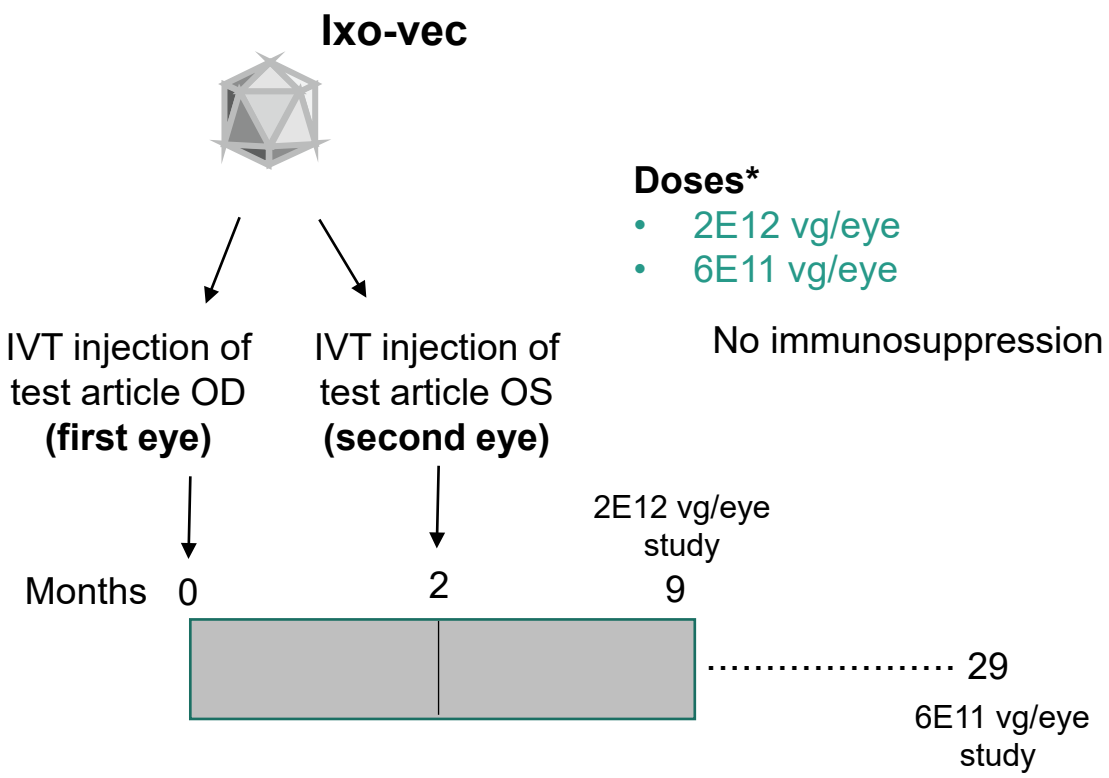
Neovascular AMD is a bilateral disease

- 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/years

Potential for immune system sensitization after first eye administration

- Increased risk of inflammation after fellow eye dose
- Loss of the gene therapy efficacy due to formation of neutralizing antibodies or anti-drug antibodies

Nonclinical data support feasibility of Ixo-vec bilateral staggered dosing to fellow eyes: *Second eye dose of Ixo-vec two months after first eye is well tolerated*



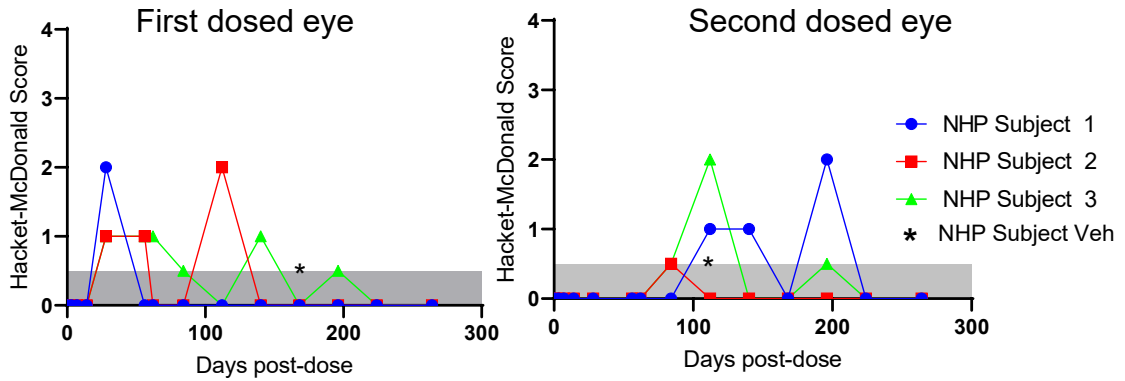
Assessments

- **Tolerability**-Ophthalmic exams
- **Humoral response-** Neutralizing antibodies (nAbs) and total antibodies (Tabs)
- **Aflibercept levels-** Vitreous collections (ELISA)

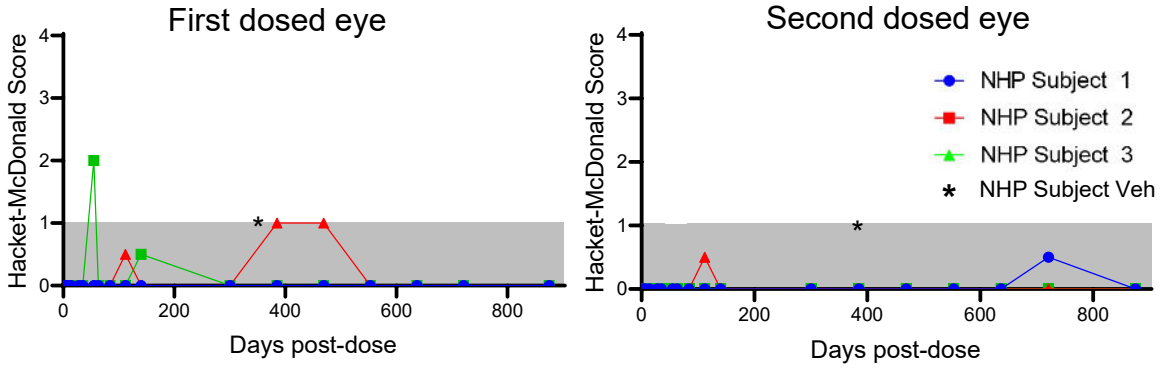
*** HED 4E12 and 1E12 vg/eye**

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)



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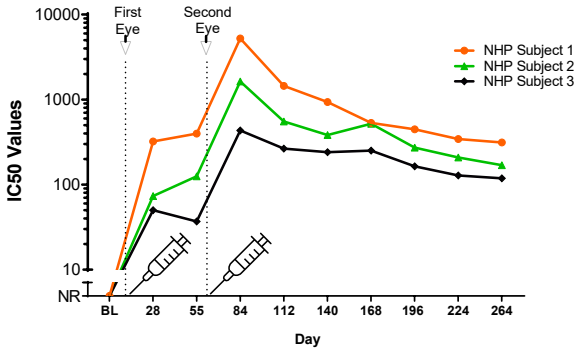
Nonclinical data support feasibility of Ixo-vec staggered dosing to fellow eyes:
Levels of aflibercept are within the range of a multitude of NHP studies of Ixo-vec

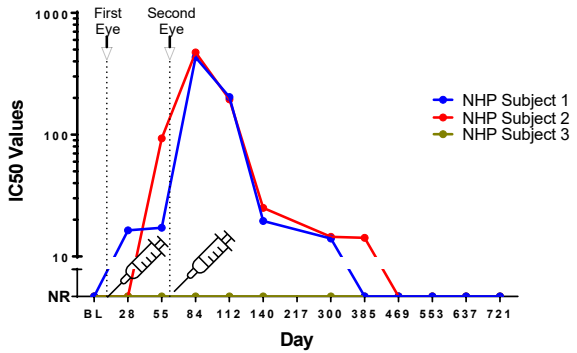
Anti-vector humoral immune response

Dose of first eye results in systemic Nab activity

2E12 vg/eye*



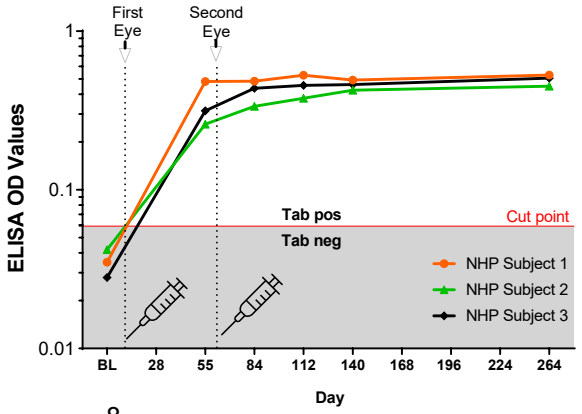
6E11 vg/eye*



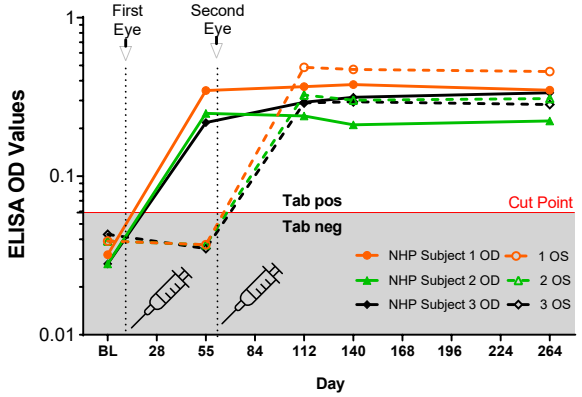
Ocular Tab levels suggests compartmentalized total antibody humoral immune response in the dosed eye

(Dose 2E12 vg/eye)*

Serum



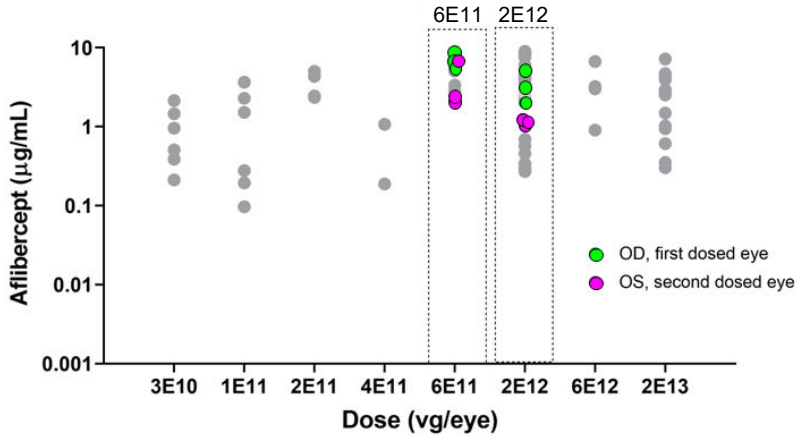
Vitreous



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

Ocular levels of aflibercept

- Staggered dosing resulted in 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

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Conclusions

Ixo-vec, a potential single administration treatment for nAMD, provides robust, durable aflibercept levels with minimal inflammation and is well tolerated with second eye administration

- GLP study with lower doses of 1E11 and 3E10 vg/eye (HED 2E11 and 6E10 vg/eye) supports dose choices for ongoing Phase II LUNA trial
  - 3E10 vg/eye (HED 6E10 vg/eye) resulted in peak aflibercept levels within the targeted therapeutic range
  - No Observed Adverse Effect Level (NOAEL) identified at 1E11 vg/eye
- NHP data suggests feasibility of Ixo-vec bilateral staggered administration
  - No exacerbated inflammation associated with staggered administration
  - Despite elevated systemic humoral response after first eye injection, second eye antibodies undetectable prior to injection
  - Peak aflibercept levels were within therapeutic range in both eyes with bilateral staggered administration

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