



Evaluation of Tolerability and Immunogenicity of EDIT-101 Following Subretinal Injection in Non- human Primates

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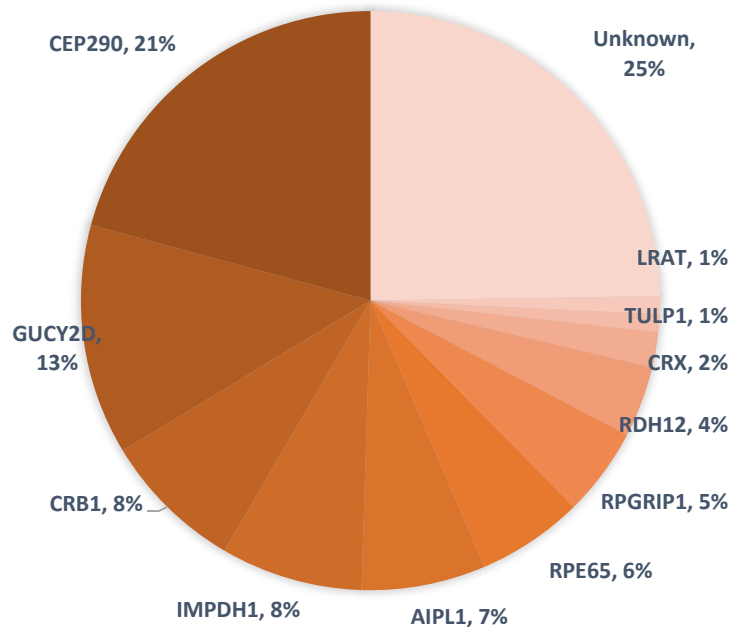
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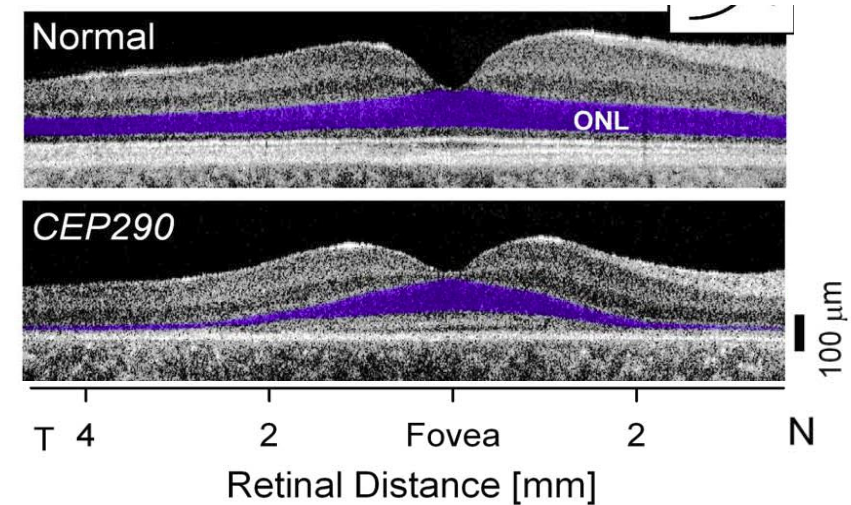
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eO | Leber Congenital Amaurosis 10 (LCA10)

- LCA is a group of heterogeneous and inherited retinal dystrophies, characterized by severe loss of vision in the first years of life
- LCA10 is caused by autosomal recessive mutations in the CEP290 gene encoding the ciliary protein necessary for photoreceptor function



Sweeney MO, Mol Vis. 2007 Apr 5;13:588-93.

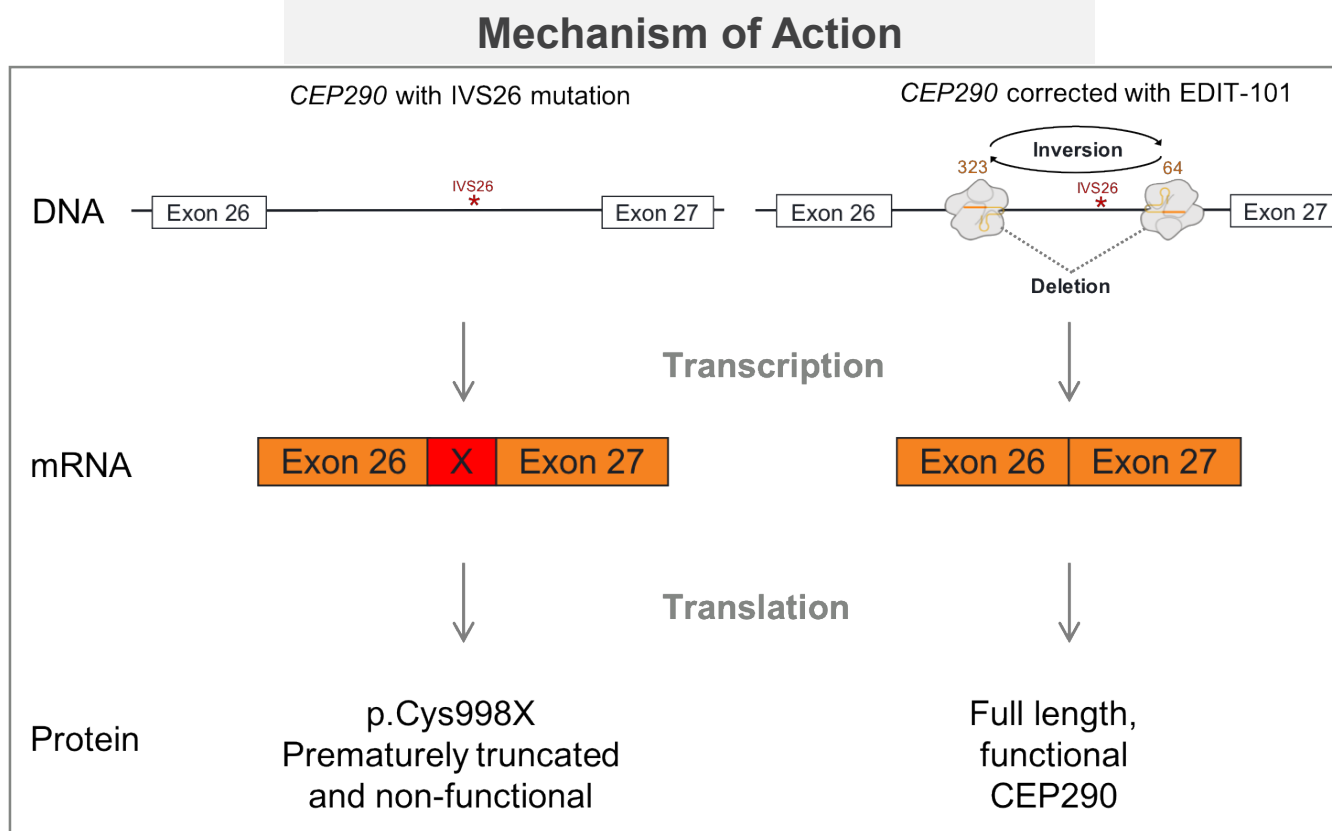
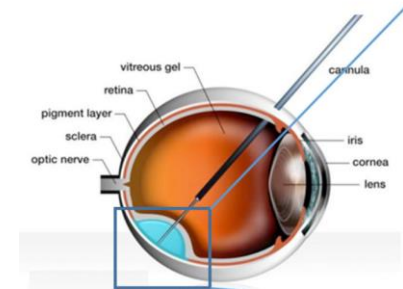
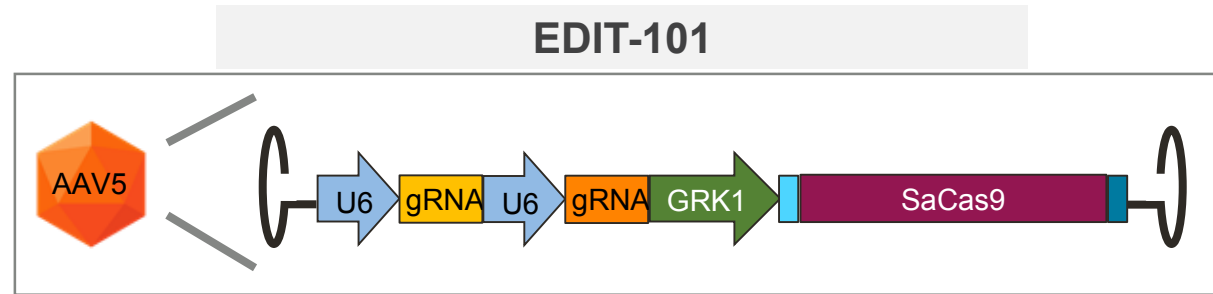


Boye et al., PLOS ONE 2014

Target: surviving foveal photoreceptors

- Despite severe loss of visual acuity, foveal cones remain and foveal thickness by OCT is similar to normal
- Normal intracranial visual pathways
- It is estimated that near-normal visual acuity can be achieved with ~10% of functioning photoreceptors^{1,2}

1. Geller, Sieving and Green, *J. Opt. Soc. Am.*, 1992;
2. Geller and Sieving, *Vision Res.*, 1993.





Ocular Tolerability Study of EDIT-101 following Subretinal Injection in Cynomolgus Macaques

TREATMENT GROUPS

Group (N=3 /group)	Treatment		Vector Dose (vg/mL) (100 uL/eye)	Methyl- Prednisolone (Day -1 to Week 4)	Study Duration (Weeks)
	Left Eye	Right Eye			
1	Vehicle	Vehicle	0	X	6
2	Vehicle	EDIT-101	1E12	X	13
3	Vehicle	EDIT-101	1E12	✓	13
4	VIR067 (Surrogate NHP vector)	VIR067	7E11	✓	6

TOLERABILITY AND SAFETY ENDPOINTS

- Ophthalmic exam and intraocular pressure measurements (OE/IOP)
- Electroretinogram (ERG): Groups 2 and 3
- Histopathology (H&E)

IMMUNOGENICITY EVALUATIONS

- Antibody (ADA) and T-cell (ELISPOT) responses to SaCas9 and AAV5 capsid

ACTIVITY ANALYSES

- Distribution of AAV vector genome by In situ hybridization (ISH)
- Expression of SaCas9 protein by Immunohistochemistry (IHC)
- On-target CEP290 gene editing by next generation sequencing: Groups 1 and 4



Subretinal Delivery of EDIT-101 and VIR067 Well Tolerated in NHPs - 1

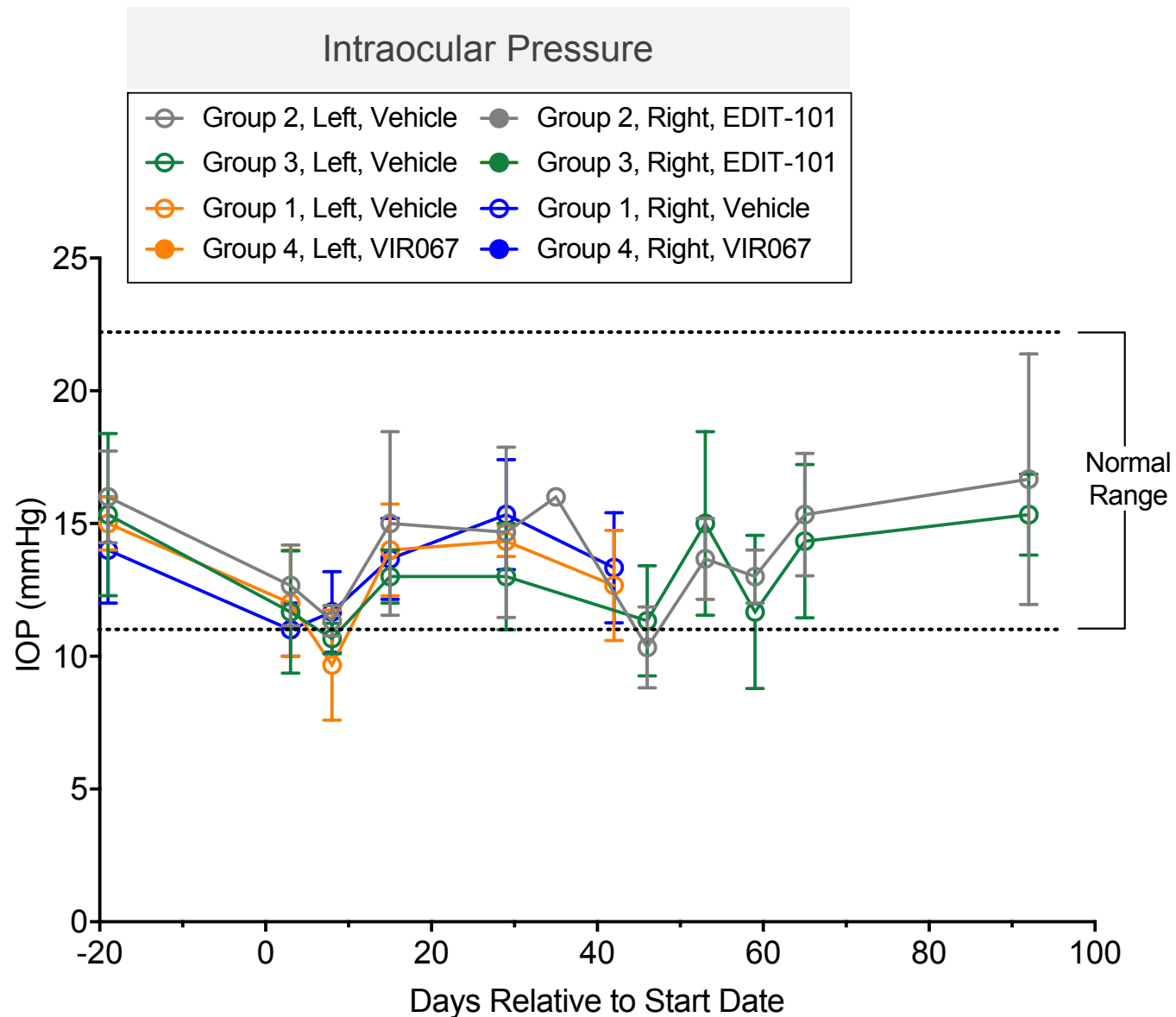
Ophthalmic Examination (Modified SUN, Hackett-McDonald & SPOTS Uveitis Scoring Systems)				
Score	Aqueous Flare	Vitreous Haze	Aqueous Cell	Vitreous Cell
0	None		No cells	≤ 1 cell
0.5	N/A	Minimal	1-5 cells	2-5 cells
1	Mild		6-25 cells	
2	Moderate		26-50 cells	
3	Marked		51-100 cells	
4	Severe		>100 cells	

Representative OE from Group 3 animals with 4 weeks of immunosuppression

Animal ID	Day(s) Relative to Start Date	Left Eye, Vehicle				Right Eye, EDIT-101			
		Aqueous Flare	Aqueous Cell	Vitreous Haze	Vitreous Cell	Aqueous Flare	Aqueous Cell	Vitreous Haze	Vitreous Cell
4	-19	0	0	0	0	0	0	0	0
	3	1	0	0	0	1	0	0	0
	8	0	0	0	1	0	0	0.5	0.5
	15	0	0	0	0	0	0	0	0
	29	0	0	0	0	0	0	0	0
	46	0	0	0	0	0	0	0	0
	53	0	0	0	0	0	0	0	0
	59	0	0	0	0	0	0	0	0
	65	0	0	0	0	0	0	0	0
	92	0	0	0	0	0	0	0	0
5	-19	0	0	0	0	0	0	0	0
	3	1	0	0	1	1	0	0	0
	8	0	0	0	1	0	0	0.5	0.5
	15	0	0	0	0.5	0	0	0	0.5
	29	0	0	0	0	0	0	0	0
	46	0	0	0	0	1	0	0	1
	53	0	0	0	0	0	0	0	0
	59	0	0	0	0	0	0	0	0
	65	0	0	0	0	0	0	0	0
	92	0	0	0	0	0	0	0	0
6	-19	0	0	0	0	0	0	0	0
	3	1	0	0	0	1	0	0	1
	8	0	0	0	0.5	0	0	0.5	1
	15	0	0	0	0	0	0	0	0
	29	0	0	0	0	0	0	0	0
	46	0	0	0	0	0	0	0	0
	53	0	0	0	0	0	0	0	0
	59	0	0	0	0	0	0	0	0
	65	0	0	0	0	0	0	0	0
	92	0	0	0	0	0	0	0	0

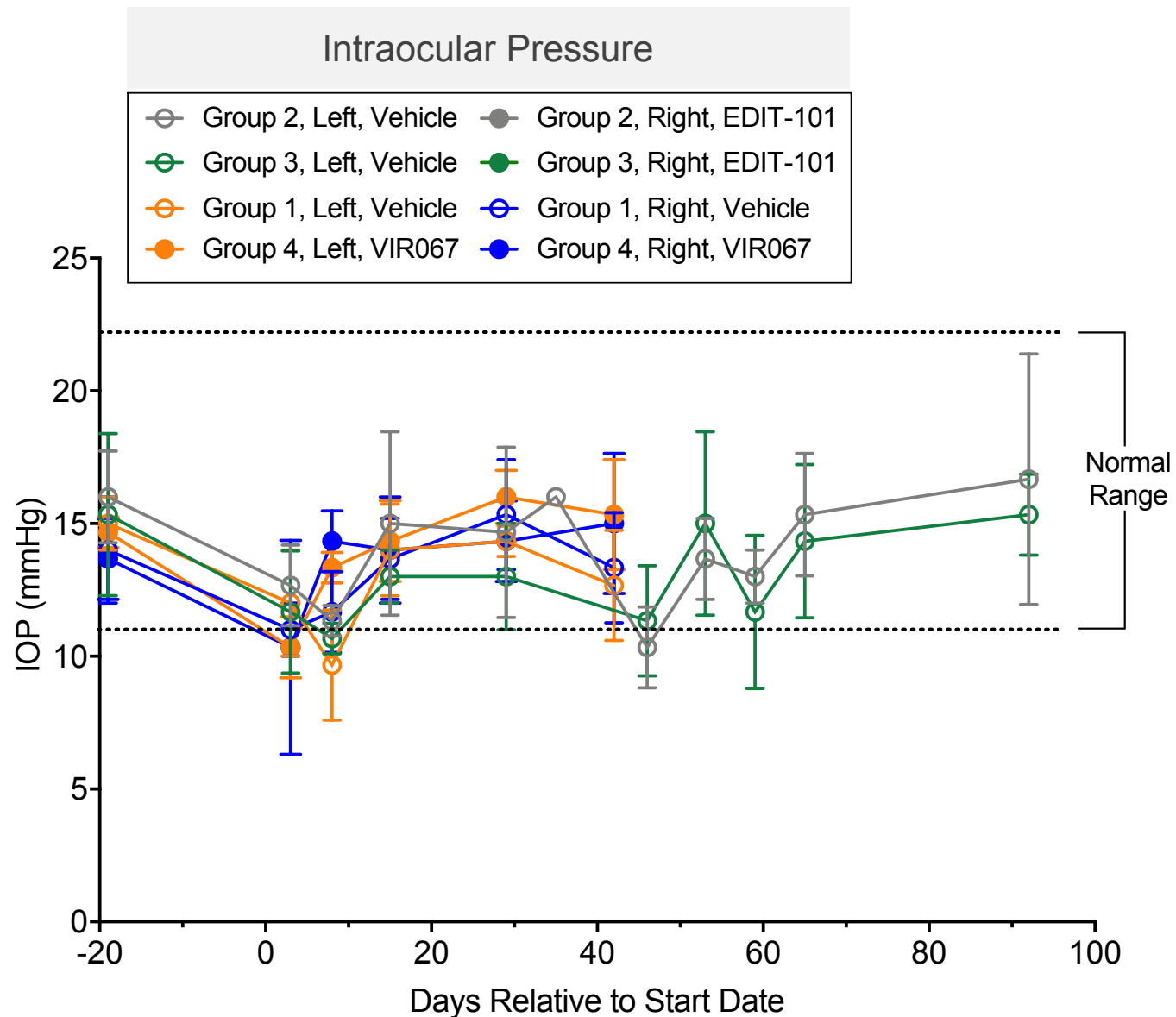


Subretinal Delivery of EDIT-101 and VIR067 Well Tolerated in NHPs - 2



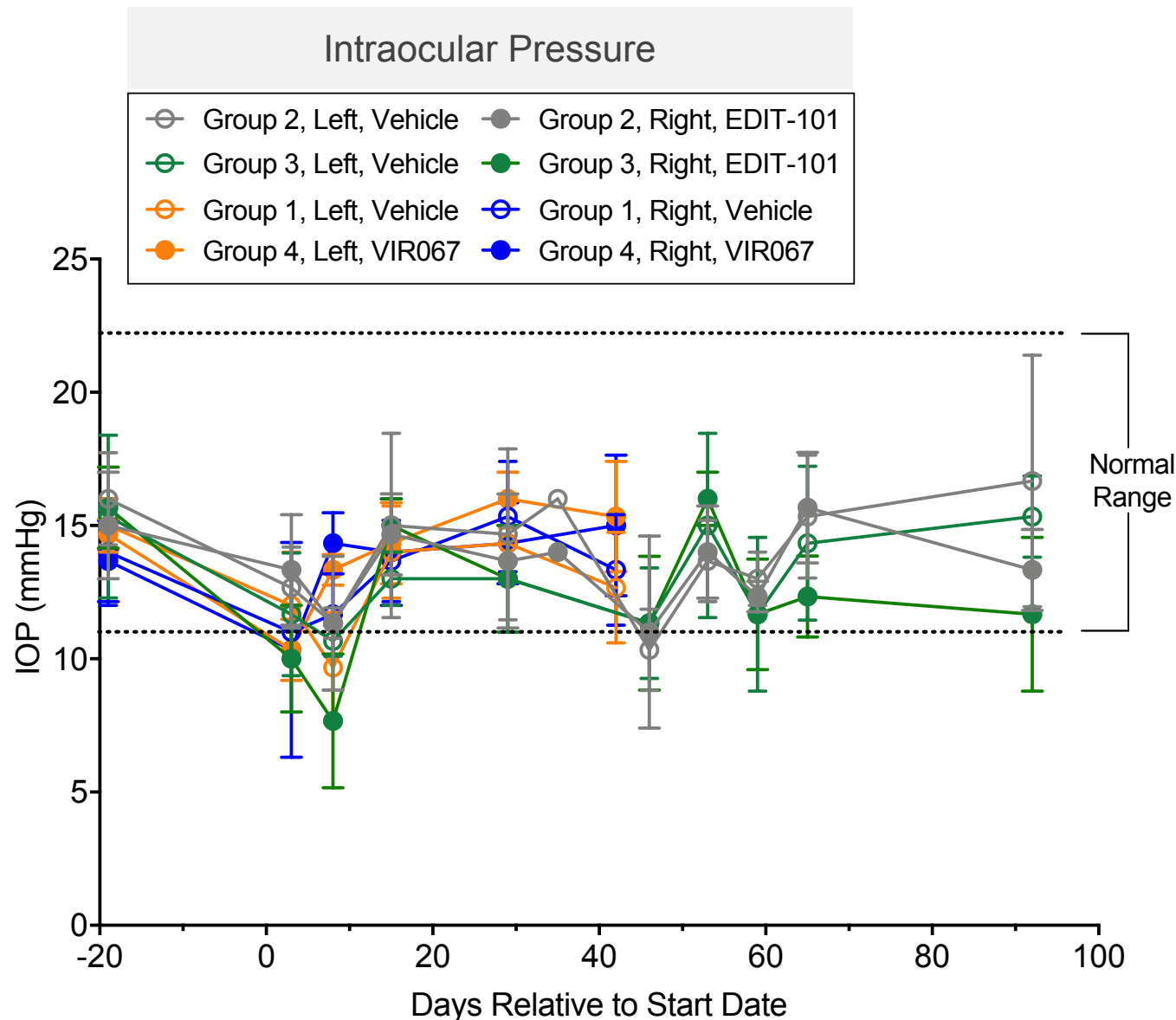


Subretinal Delivery of EDIT-101 and VIR067 Well Tolerated in NHPs - 2





Subretinal Delivery of EDIT-101 and VIR067 Well Tolerated in NHPs - 2



SUMMARY

- Surgical procedure-related responses were minimal/mild and transient
 - Comparable between vehicle- and test article-treated eyes
- No delayed inflammation in EDIT-101 treated eyes following the discontinuation of steroids
- Comparable IOP between vehicle- and test article-treated eyes



Delayed Mild Inflammation Observed in Non-immunosuppressed NHPs

Animal ID	Day(s) Relative to Start Date	Left Eye, Vehicle				Right Eye, EDIT-101			
		Aqueous Flare	Aqueous Cell	Vitreous Haze	Vitreous Cell	Aqueous Flare	Aqueous Cell	Vitreous Haze	Vitreous Cell
1	-19	0	0	0	0	0	0	0	0
	3	1	0	0	0	1	0	0	0
	8	0	0	0	0	0	0	0.5	1
	15	0	0	0	0	0	0	0	0.5
	29*	1	0	0	0	2	1	1	0
	35	0	0	0	0	1	0	0	0
	46	0	0	0	0	0	0	0	0
	53*	0	0	0	0	0	0	0	0
	59	0	0	0	0	0	0	0	0
	65	0	0	0	0	0	0	0	0
2	-19	0	0	0	0	0	0	0	0
	3	1	0	0	0	1	0	0	0
	8	0	0	0	1	0	0	0.5	1
	15	0	0	0	0	0	0	0	0.5
	29	0	0	0	0	0	0	0	0
	46*	0	0	0	0	0	0	0	0
	53*	0	0	0	0	0	0	0	0
	59	0	0	0	0	0	0	0	0
	65	0	0	0	0	0	0	0	0
	92	0	0	0	0	0	0	0	0
3	-19	0	0	0	0	0	0	0	0
	3	1	0	0	0	1	0	0	0
	8	0	0	0	0	0	0	0.5	1
	15	0	0	0	0	0	0	0	0.5
	29	0	0	0	0	0	0	0	0
	46*	0	0	0	0	0	0	0	0
	53*	0	0	0	0	0	0	0	0
	59	0	0	0	0	0	0	0	0
	65	0	0	0	0	0	0	0	0
	92	0	0	0	0	0	0	0	0

Additional Ophthalmic Exam Findings

EDIT-101 treated right eye:

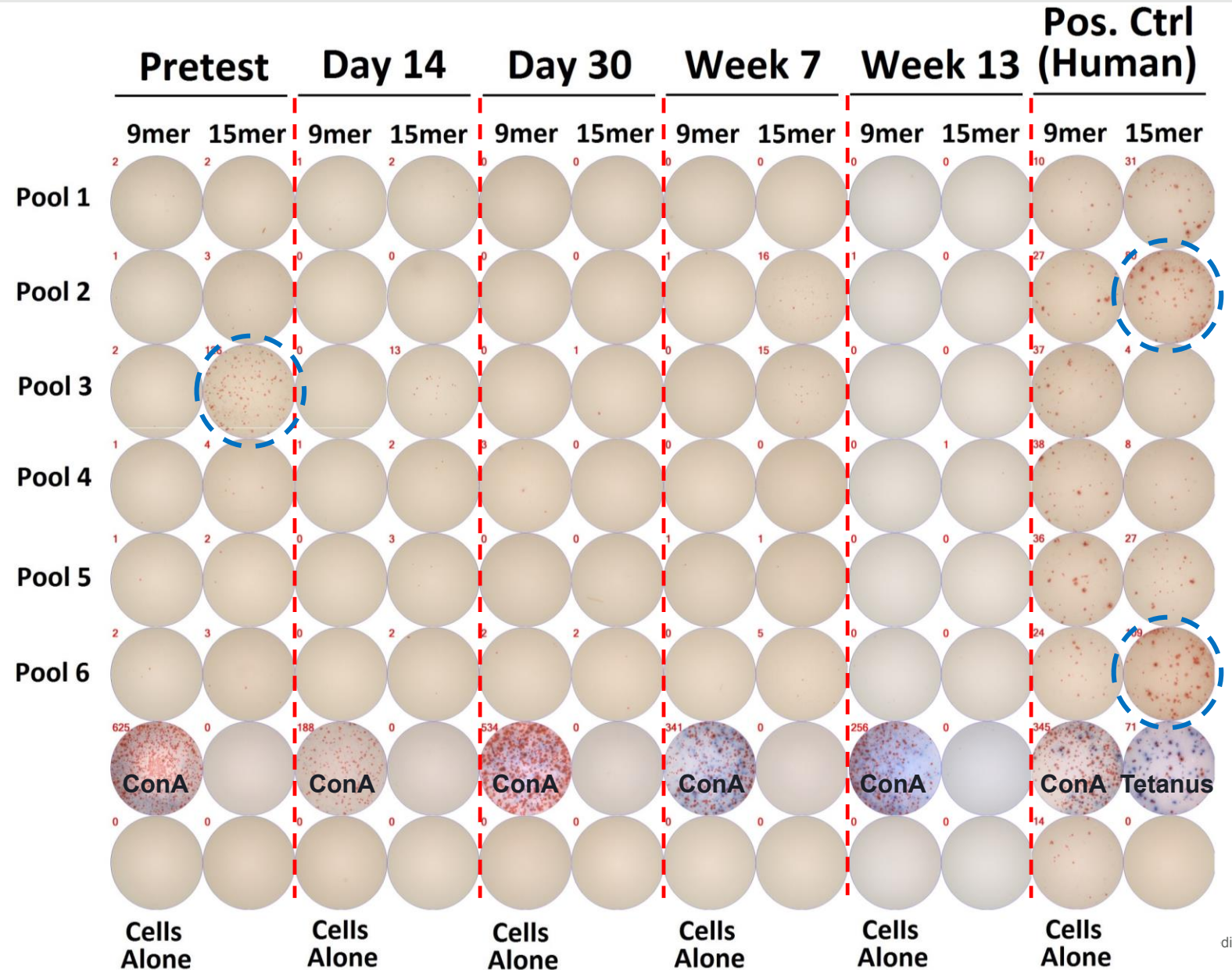
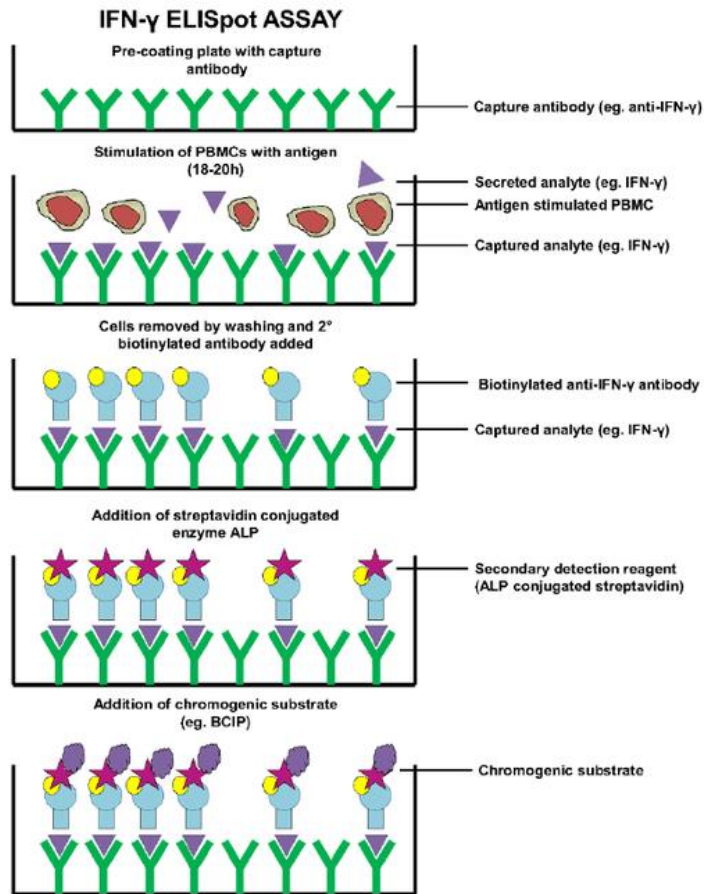
*D29: Mild uveitis

*D46/D53: Mild chorioretinitis (perivascular sheathing, cellular infiltrates within subretinal bleb)

OE from Group 2 animals without 4 weeks of immunosuppression



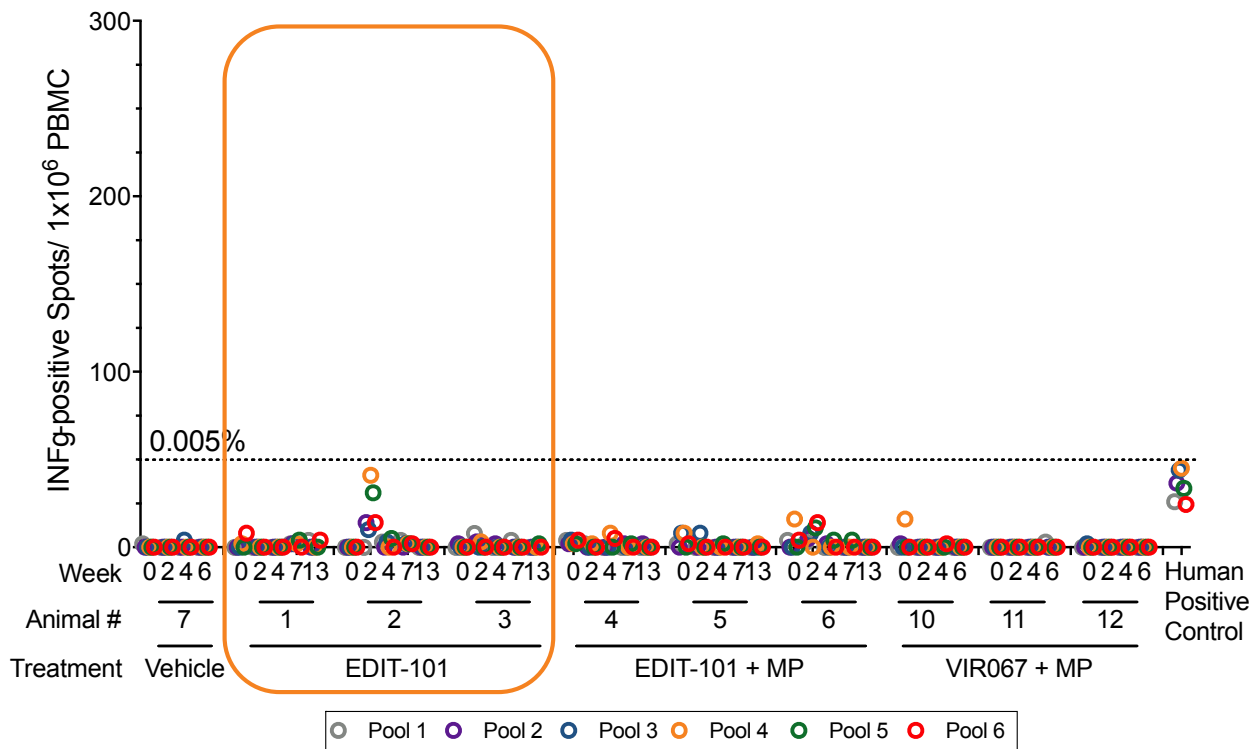
Assessing SaCas9-specific T-Cell Responses in NHP PBMC by ELISPOT





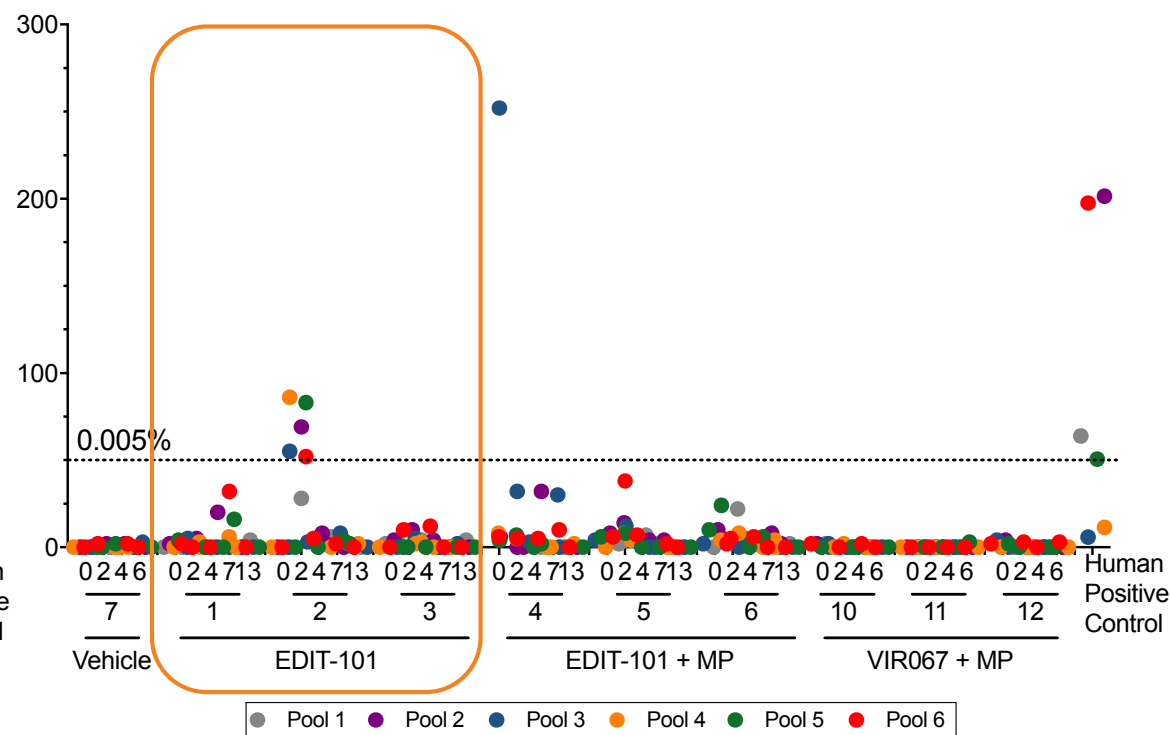
Delayed Ocular Inflammation Not Correlated with SaCas9-specific T-cells

ELISPOT Assessing CD8+ T Cell Response to SaCas9 Peptide Antigens (9-mer)



No significant pre-existing or treatment-induced CD8+ T-cell responses to SaCas9 in NHP

ELISPOT Assessing CD4+ T Cell Response to SaCas9 Peptide Antigens (15-mer)

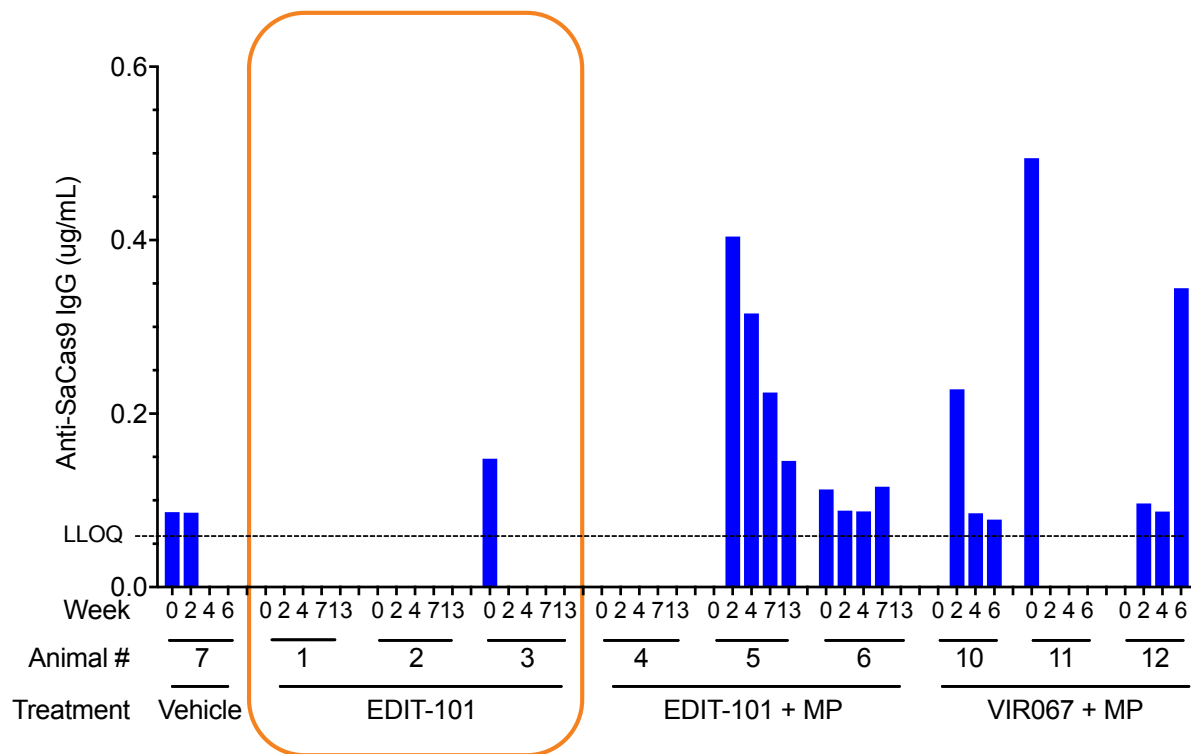


- Pre-existing SaCas9-specific CD4+ T-cell response detected in 1 out of 12 NHPs
- Transient and marginal CD4+ T-cell response induced in 1 out of 3 non-immunosuppressed NHPs treated with EDIT-101



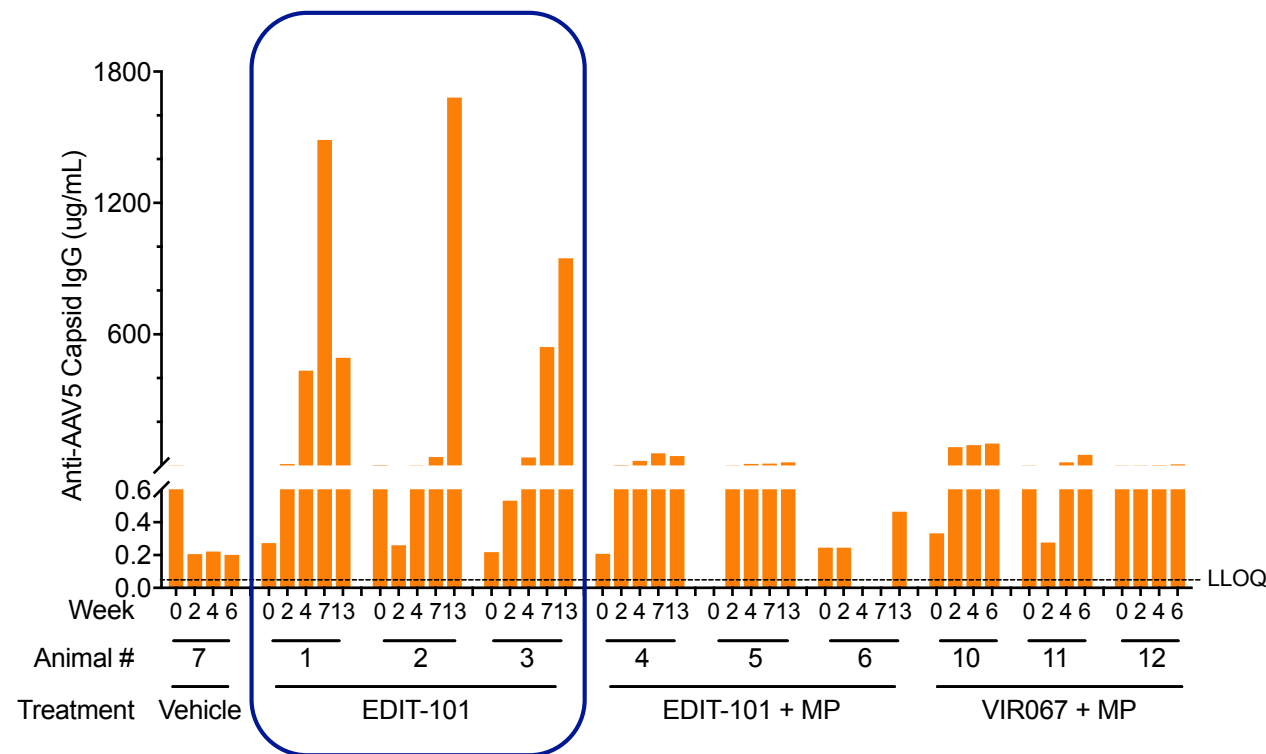
Robust Immune Response to AAV5 May Contribute to Delayed Ocular Inflammation in Non-immunosuppressed NHPs

Anti-SaCas9 Ab ELISA



Low levels of Anti-SaCas9 Ab not correlated with delayed ocular inflammation observed in non-immunosuppressed animals (EDIT-101)

Anti-AAV5 Capsid Ab ELISA



Anti-AAV5 capsid Ab response detected in both EDIT-101 and VIR067-treated NHPs, most robust in non-immunosuppressed animals (EDIT-101)



Activity of VIR067 in NHP in the Presence of Host Immune Responses

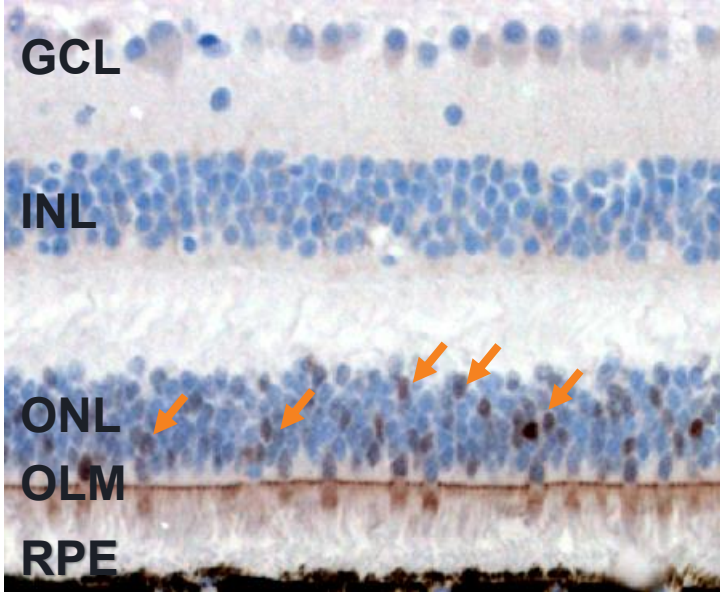
Immune Responses

Vector Dose (vg/mL)	Anti-AAV5 Ab	Anti-Cas9 Ab	Cas9-specific T-cells
1E11			
3E11			
6E11	3/3	2/3	0/3
1E12			
3E12			

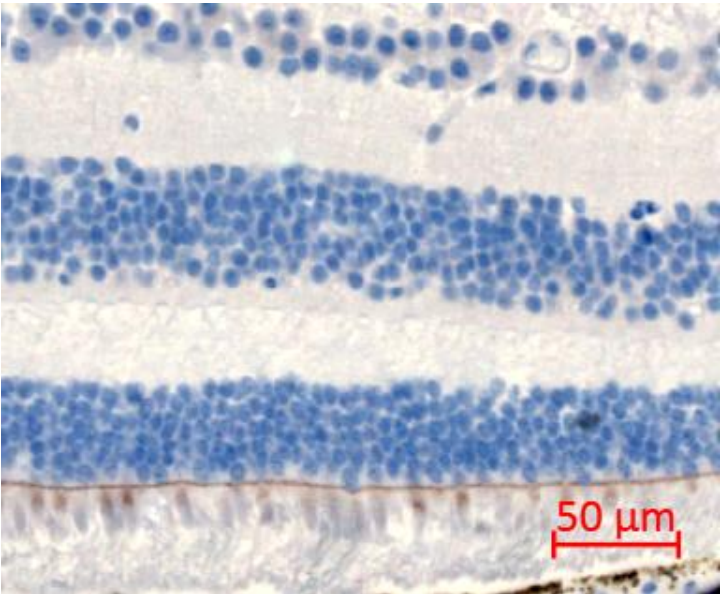
AAV ISH

CAS9 IHC

VIR067



Vehicle





Comparable Activity of VIR067 in NHP and EDIT-101 in HuCEP290 KI Mice

Immune Responses				Productive Editing Rates in Photoreceptors	
Vector Dose (vg/mL)	Anti-AAV5 Ab	Anti-Cas9 Ab	Cas9-specific T-cells	Surrogate NHP vector in NHP (%) Mean ± SD (n=3)	EDIT-101 in HuCEP290 KI Mice (%) Mean ± SD (n=13-51)
1E11	2/3	1/3		3.5 ± 5.5	5.5 ± 4.1
3E11					14.8 ± 10.6
6E11	3/3	2/3	0/3	16 ± 2.8	15.7 ± 11.5
1E12	3/3	2/3		27.9 ± 20.7	44.2 ± 20.3
3E12					60.8 ± 30.2

OCULAR TOLERABILITY

- Subretinal dosing of EDIT-101 and surrogate VIR067 were well-tolerated in NHP
- Delayed mild ocular inflammation was observed in non-immunosuppressed NHPs
 - resolved following local or systemic steroid treatment
- Prophylactic treatment with systemic steroids effectively prevented vector-related ocular inflammation

IMMUNOGENICITY

- Low levels of pre-existing or induced SaCas9-specific Ab and T-cell responses did not correlate with delayed ocular inflammation
- Robust anti-AAV5 immunity likely contributed to delayed ocular inflammation
- Neither pre-existing nor induced SaCas9- and AAV5-specific immunity impacted the pharmacological activity of the vector

See also “Gene Editing Specificity Assessment for EDIT-101, an LCA10 Therapeutic Candidate” by Wilson, C et al, Poster #906 @ 5:45 – 7:45 pm on Friday, May 18



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