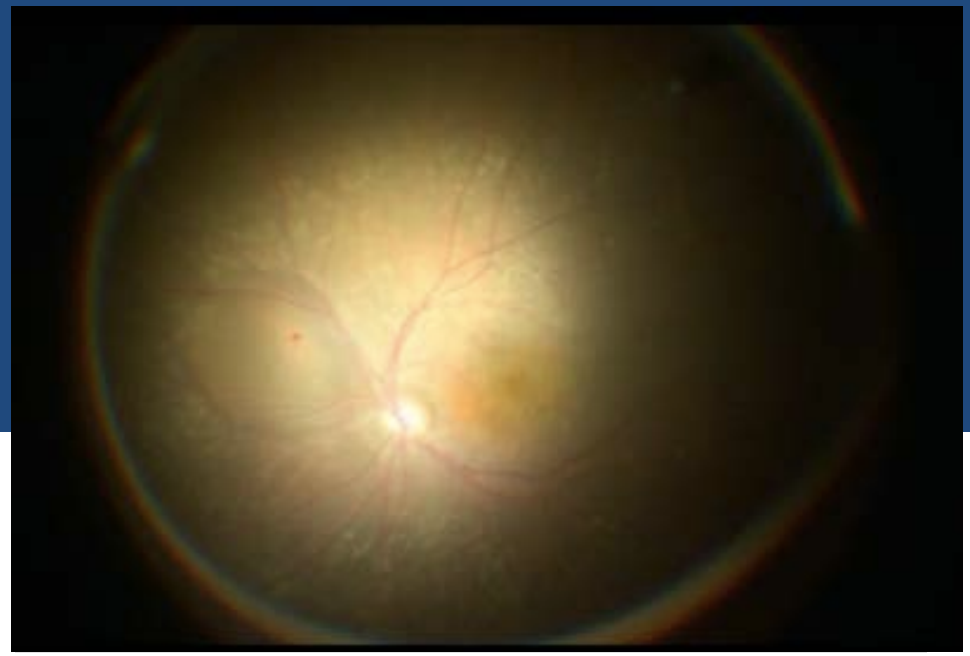

Six Month Results of the Phase I Study to Evaluate Safety & Tolerability of RGX-314 Gene Therapy in nAMD Subjects

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10/26/2018

Disclosures

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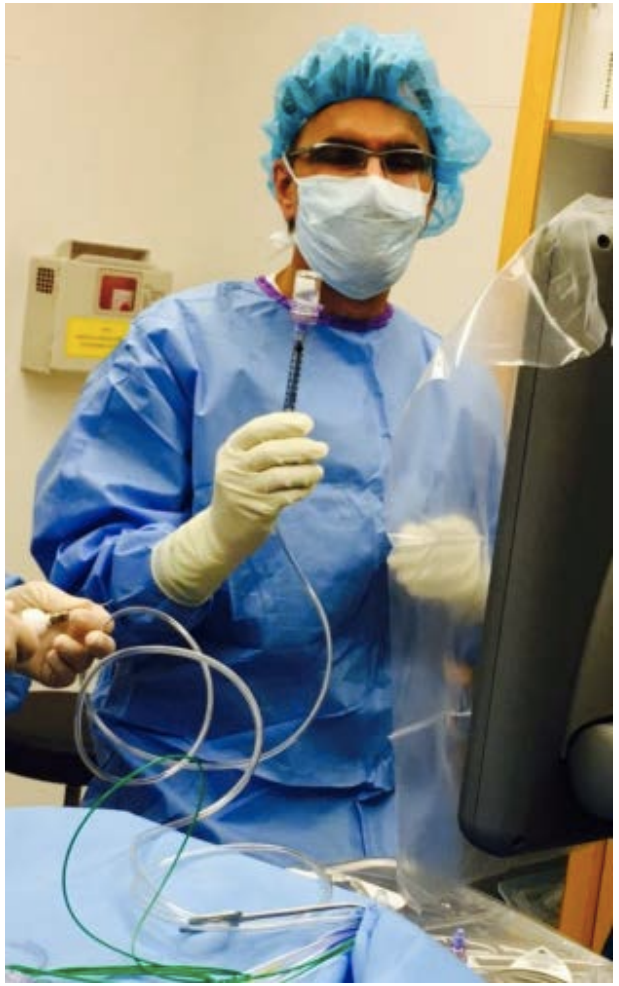
Board of Directors: Ocular Therapeutix

Equity: Allegro, Adverum, jCyte, Ocular Therapeutix



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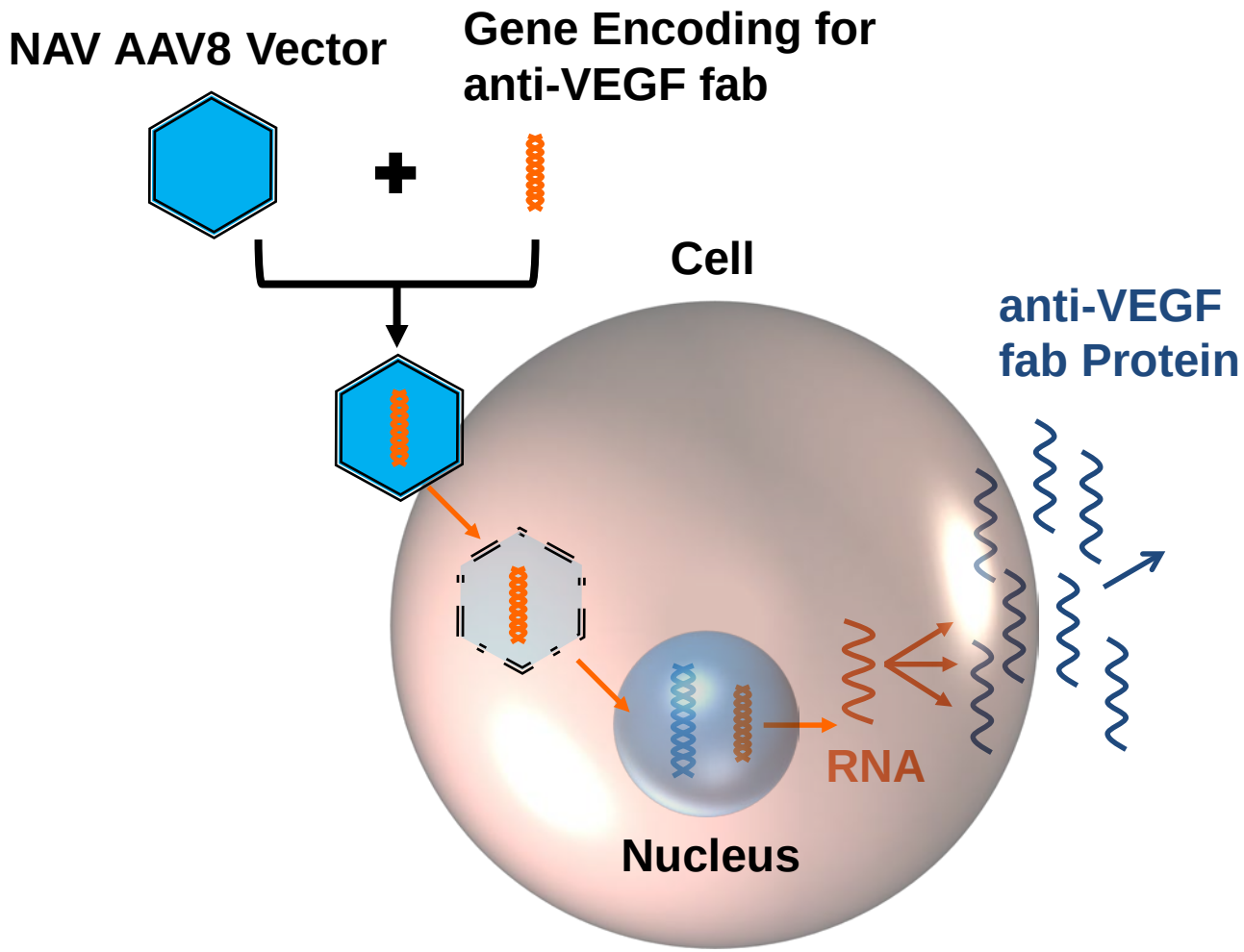
EXCELLENCE IN EYE CARE

RGX-314: Optimized NAV® Gene Therapy for Wet AMD

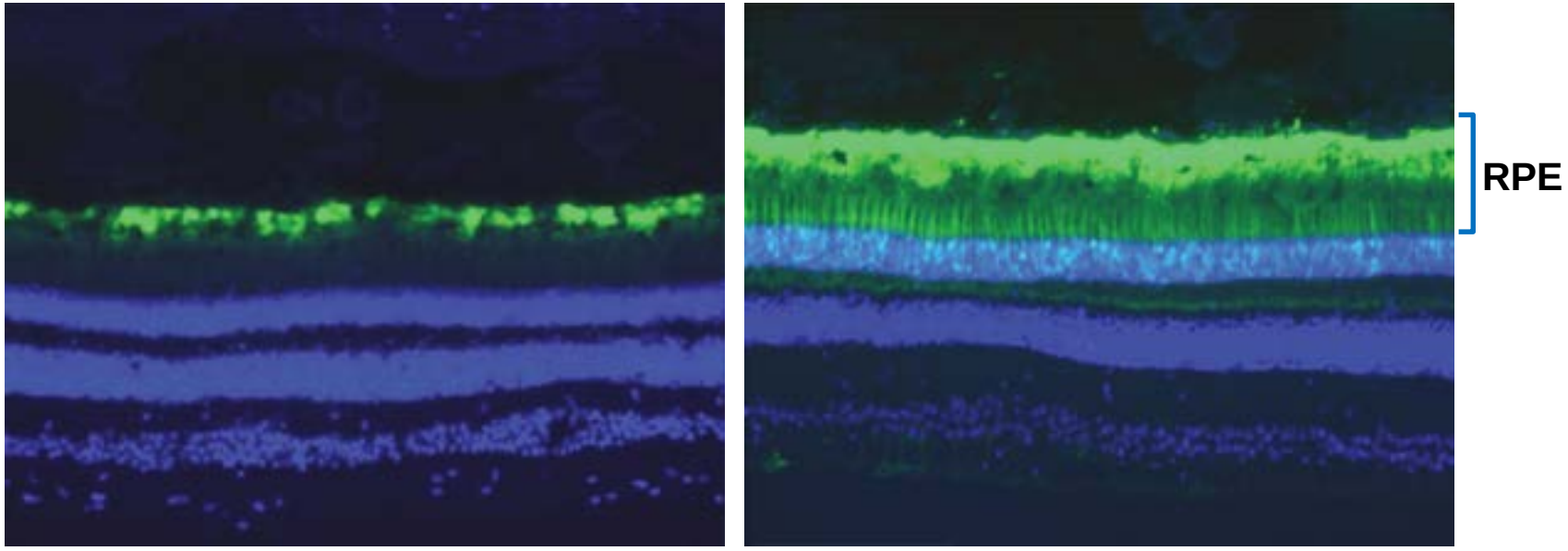
RGX-314 is Designed to Deliver a Gene Encoding for an anti-VEGF fab Protein



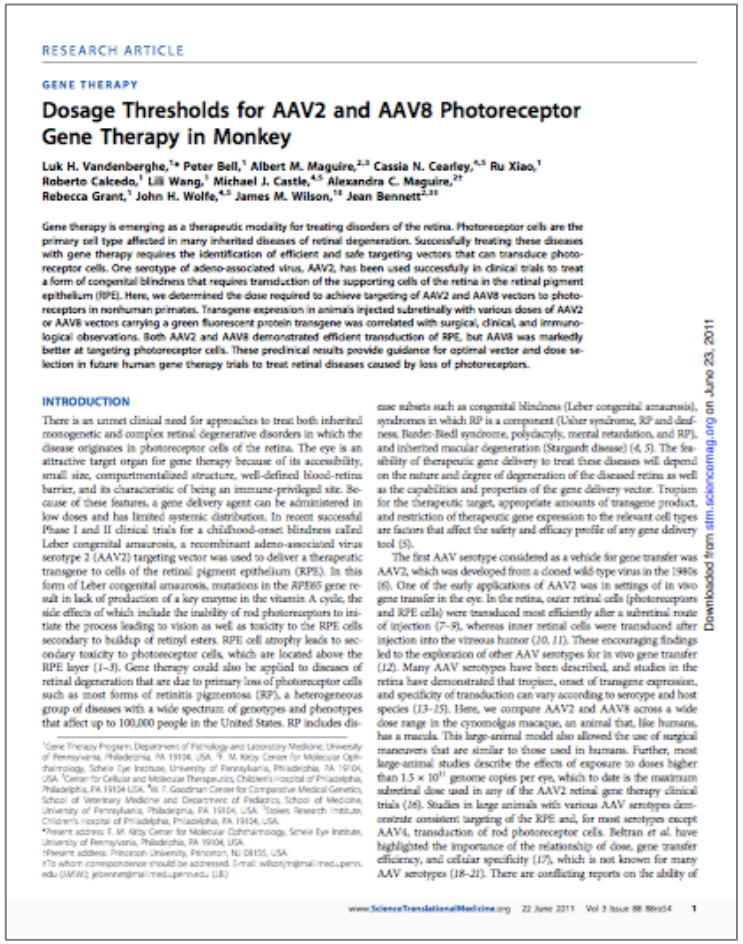
RGX-314: Utilizing AAV8 for Higher Protein Expression in NHPs

AAV2

AAV8



More Efficient Gene Delivery to the RPE[1]



RESEARCH ARTICLE

GENE THERAPY

Dosage Thresholds for AAV2 and AAV8 Photoreceptor Gene Therapy in Monkey

Luk H. Vandenberghe,[1]* Peter Bell,[1] Albert M. Maguire,[2,3] Cassia N. Cearley,[4,5] Ru Xiao,[1] Roberto Calcedo,[1] Lili Wang,[1] Michael J. Castle,[4,5] Alexandra C. Maguire,[2†] Rebecca Grant,[1] John H. Wolfe,[4,5] James M. Wilson,[1‡] Jean Bennett[2,3‡]

Gene therapy is emerging as a therapeutic modality for treating disorders of the retina. Photoreceptor cells are the primary cell type affected in many inherited diseases of retinal degeneration. Successfully treating these diseases with gene therapy requires the identification of efficient and safe targeting vectors that can transduce photoreceptor cells. One serotype of adeno-associated virus, AAV2, has been used successfully in clinical trials to treat a form of congenital blindness that requires transduction of the supporting cells of the retina in the retinal pigment epithelium (RPE). Here, we determined the dose required to achieve targeting of AAV2 and AAV8 vectors to photoreceptors in nonhuman primates. Transgene expression in animals injected subretinally with various doses of AAV2 or AAV8 vectors carrying a green fluorescent protein transgene was correlated with surgical, clinical, and immunological observations. Both AAV2 and AAV8 demonstrated efficient transduction of RPE, but AAV8 was markedly better at targeting photoreceptor cells. These preclinical results provide guidance for optimal vector and dose selection in future human gene therapy trials to treat retinal diseases caused by loss of photoreceptors.

INTRODUCTION

There is an unmet clinical need for approaches to treat both inherited monogenetic and complex retinal degenerative disorders in which the disease originates in photoreceptor cells of the retina. The eye is an attractive target organ for gene therapy because of its accessibility, small size, compartmentalized structure, well-defined blood-retina barrier, and its characteristic of being an immune-privileged site. Because of these features, a gene delivery agent can be administered in low doses and has limited systemic distribution. In recent successful Phase I and II clinical trials for a childhood-onset blindness called Leber congenital amaurosis, a recombinant adeno-associated virus serotype 2 (AAV2) targeting vector was used to deliver a therapeutic transgene to cells of the retinal pigment epithelium (RPE). In this form of Leber congenital amaurosis, mutations in the *RPE65* gene result in lack of production of a key enzyme in the vitamin A cycle, the side effects of which include the inability of rod photoreceptors to initiate the process leading to vision as well as toxicity to the RPE cells secondary to buildup of retinyl esters. RPE cell atrophy leads to secondary toxicity to photoreceptor cells, which are located above the RPE layer (*1*–*3*). Gene therapy could also be applied to diseases of retinal degeneration that are due to primary loss of photoreceptor cells such as most forms of retinitis pigmentosa (RP), a heterogeneous group of diseases with a wide spectrum of genotypes and phenotypes that affect up to 100,000 people in the United States. RP includes disease subsets such as congenital blindness (Leber congenital amaurosis), syndromes in which RP is a component (Usher syndrome, RP and deafness; Bardet-Biedl syndrome, polydactyly, mental retardation, and RP), and inherited macular degeneration (Stargardt disease) (*4*, *5*). The feasibility of therapeutic gene delivery to treat these diseases will depend on the nature and degree of degeneration of the diseased retina as well as the capabilities and properties of the gene delivery vector. Tropism for the therapeutic target, appropriate amounts of transgene product, and restriction of therapeutic gene expression to the relevant cell types are factors that affect the safety and efficacy profile of any gene delivery tool (*5*).

The first AAV serotype considered as a vehicle for gene transfer was AAV2, which was developed from a cloned wild-type virus in the 1980s (*6*). One of the early applications of AAV2 was in settings of in vivo gene transfer in the eye. In the retina, outer retinal cells (photoreceptors and RPE cells) were transduced most efficiently after a subretinal route of injection (*7*–*9*), whereas inner retinal cells were transduced after injection into the vitreous humor (*10*, *11*). These encouraging findings led to the exploration of other AAV serotypes for in vivo gene transfer (*12*). Many AAV serotypes have been described, and studies in the retina have demonstrated that tropism, onset of transgene expression, and specificity of transduction can vary according to serotype and host species (*13*–*15*). Here, we compare AAV2 and AAV8 across a wide dose range in the cynomolgus macaque, an animal that, like humans, has a macula. This large-animal model also allowed the use of surgical maneuvers that are similar to those used in humans. Further, most large-animal studies describe the effects of exposure to doses higher than 1.5×10^{11} genome copies per eye, which to date is the maximum subretinal dose used in any of the AAV2 retinal gene therapy clinical trials (*16*). Studies in large animals with various AAV serotypes demonstrate consistent targeting of the RPE and, for most serotypes except AAV4, transduction of rod photoreceptor cells. Beltran *et al.* have highlighted the importance of the relationship of dose, gene transfer efficiency, and cellular specificity (*17*), which is not known for many AAV serotypes (*18*–*21*). There are conflicting reports on the ability of

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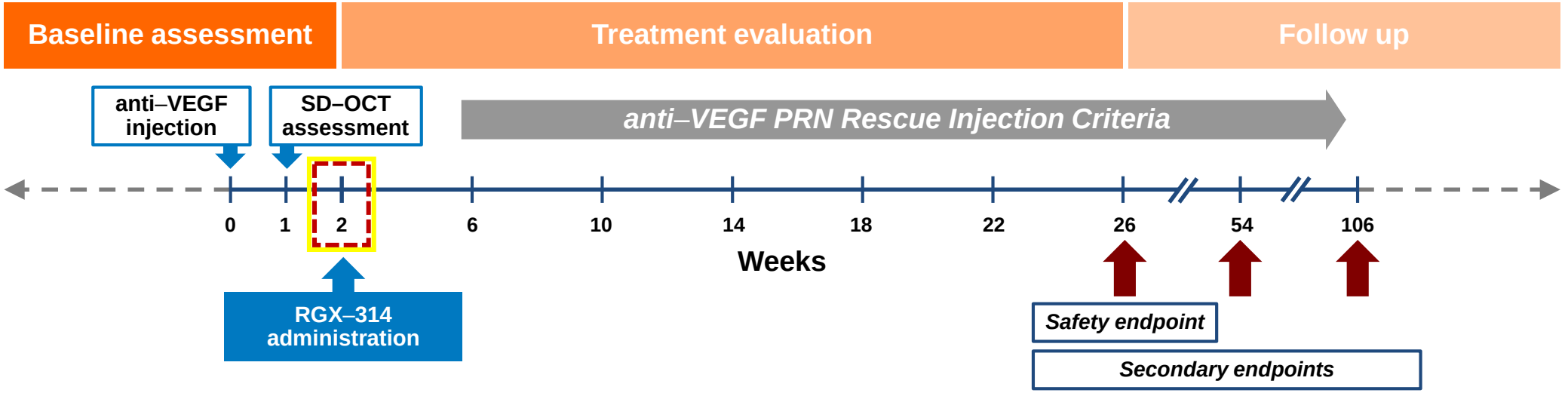
[1]Vandenberghe et al. 2011 *Science Translational Medicine*

RGX-314 Phase I Trial: Design



Previously Treated Subjects Requiring Frequent Injections

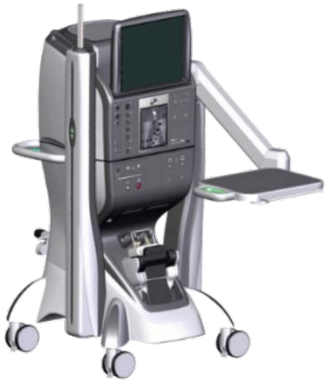
Dose 1 n = 6	Safety review[1]	Dose 2 n = 6	Safety review[1]	Dose 3 n = 6	Safety review[1]	Dose 4 n = 6
3x10^{9} GC/eye		*1x10^{10} GC/eye*		*6x10^{10} GC/eye*		*1.6x10^{11} GC/eye*

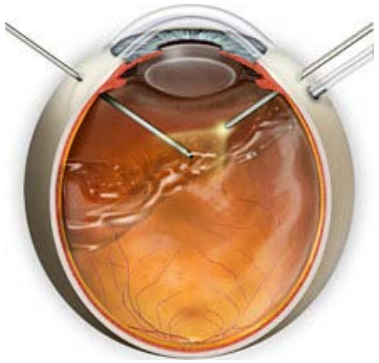
Dosing Completed in Four Cohorts

[1] Dose escalation safety review to occur four weeks after final subject in each cohort has been dosed

RGX-314: Standardized Automated Subretinal Delivery Procedure

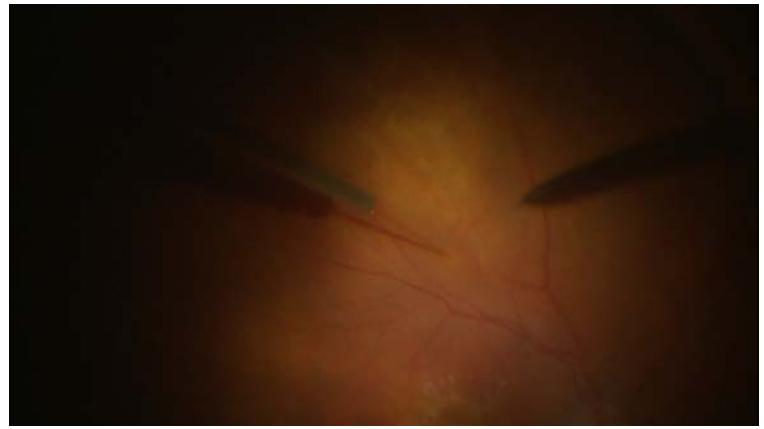
Step 1 – Vitrectomy





Step 2 – Subretinal Injection

MedOne MicroDose Syringe



Performed Under Local Anaesthesia in the OR

- Standard **small gauge** vitrectomy to perform a core vitrectomy
- Automated delivery with a **MedOne subretinal cannula** attached to the vitrectomy machine
- **Inject 250µl** to create subretinal bleb in a healthy area of retina
- Target superior to the superotemporal arcade vessel or outside the arcades
- Can create another **bleb** area if needed
- Keep margin of the bleb at least 2DA **away from the fovea**

Air fluid exchange and then **Sub-conj steroids** at the end of procedure
No positioning mandated and patient is discharged home with follow-up the next day

RGX-314 Phase I Trial: Outcome Measures and Eligibility Criteria

Objectives

Primary

- To determine the safety and tolerability of RGX-314 in patients with nAMD though 6 months

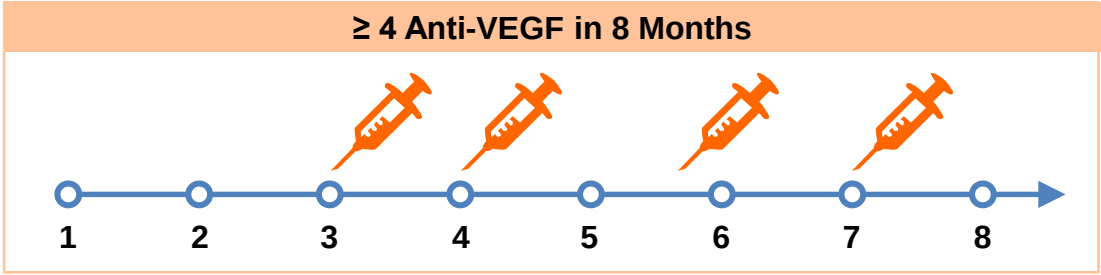
Secondary

- Expression of RGX-314 protein in the eye
- Effect of RGX-314 on best corrected visual acuity (BCVA) and central retinal thickness (CRT)
- Additional anti-VEGF injections post-RGX-314 (“Rescue”)

Rescue: New or Persistent Fluid/ Loss in Vision

- Per the Investigator's discretion

Key Inclusion Criteria



- Documented **nAMD with response to anti-VEGF at trial entry**
- Vision of 20/63 to 20/400 for the initial patient, then **20/40 to 20/400** for the rest of each cohort
- Pseudophakic (status post cataract surgery)

Subjects: 24 Patients dosed

- **7 study sites** across the United States

RGX-314 Phase I Trial: Anti-VEGF Rescue Injection Criteria

Anti-VEGF may be given beginning 4 weeks post-treatment and **PRN every 4 weeks** thereafter **per investigator's discretion** if one or more of the criteria apply:

CNV-related increased, new, or persistent fluid	Vision loss of ≥5 letters associated w/ accumulation of fluid	New ocular hemorrhage

RGX-314 Phase I Trial: Baseline Demographics for Cohorts 1-3

	Variable	Cohort 1 (n=6)	Cohort 2 (n=6)	Cohort 3 (n=6)	Total (n=18)
DEMOGRAPHICS	**Mean Age (Years)**	**78.2**	**78.0**	**80.0**	**78.7**
	Female (Number, %)	**4** (66.7%)	**3** (50.0%)	**2** (33.3%)	**9** (50.0%)
	Caucasian, no. (%)	**6** (100.0%)	**6** (100.0%)	**6** (100.0%)	**18** (100.0%)
BASELINE CHARACTERISTICS	**Months Since First anti-VEGF Injection**	**53.5**	**59.3**	**71.6**	**61.5**
	# Injections Since Diagnosis (Mean)	**40.7**	**32.5**	**34.2**	**35.8**

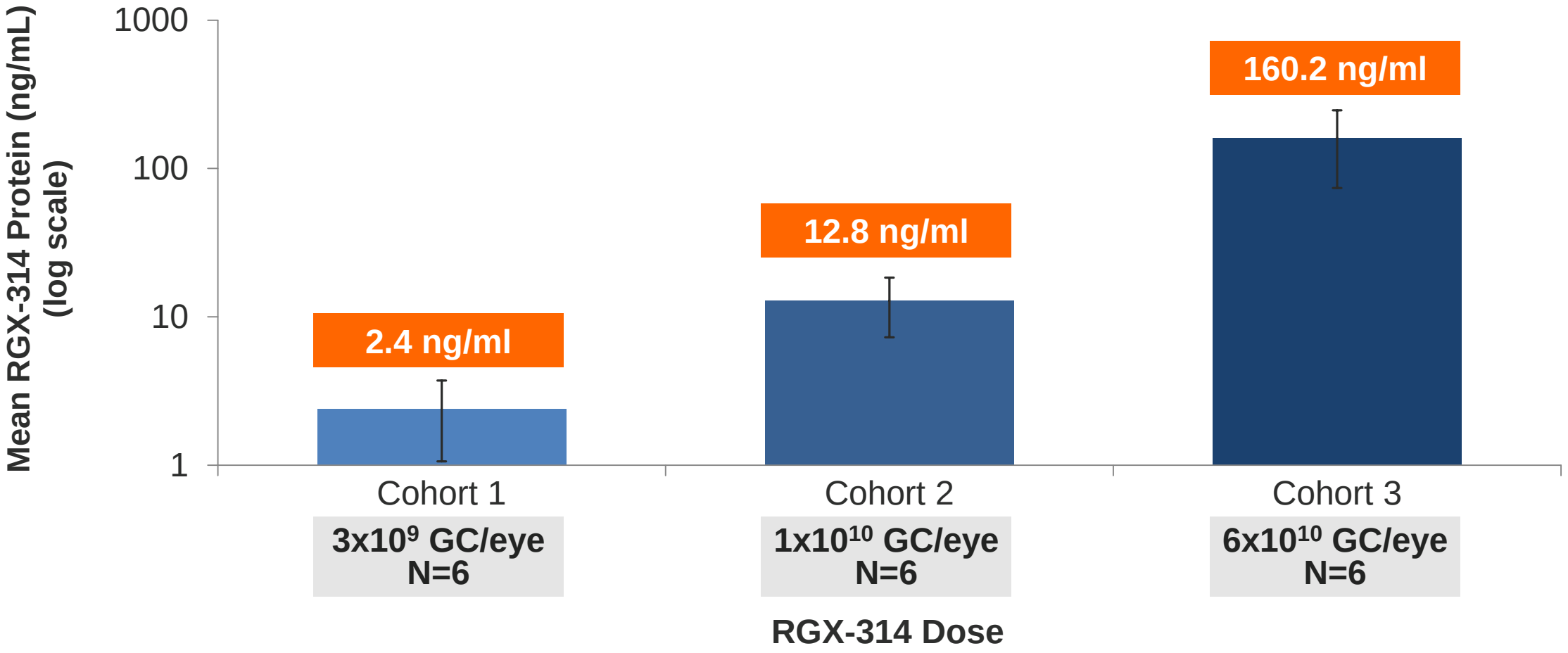
RGX-314 Phase I Trial: Safety for Cohorts 1-3*

- RGX-314 was **well-tolerated** (n=18)
- **No drug-related AEs or drug-related SAEs**
- Most AEs were assessed as mild (Grade 1 – 83%)
- **No observed clinically-determined immune responses,** drug-related ocular inflammation, or any post-surgical inflammation beyond what is expected following routine vitrectomy
- **Five SAEs that were not drug-related were reported in three subjects**
  - One subject with a peripheral retinal detachment which was repaired and resolved without sequelae
  - One subject with a hospitalization related to a pre-existing condition that resulted in death
  - One subject with an event assessed mild in severity with no relationship to RGX-314

* Data cut July 27th, 2018

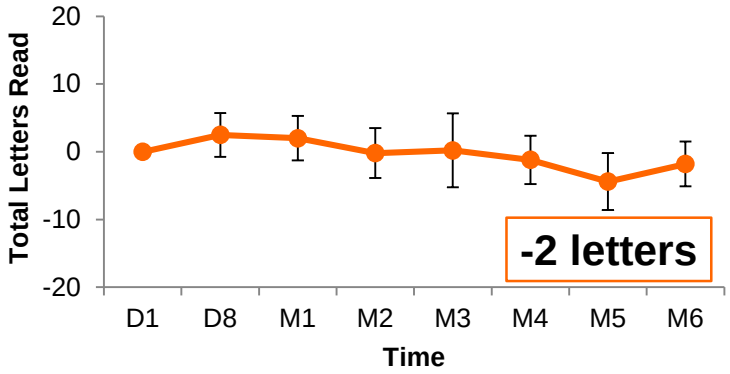
RGX-314 Phase I Trial: Protein Levels at One Month for Cohorts 1-3

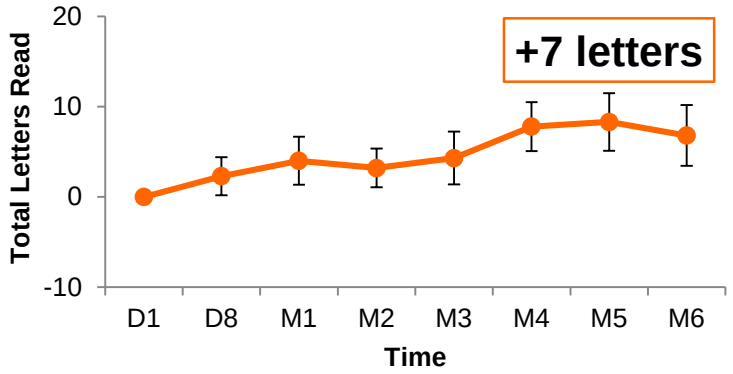
As measured from aqueous samples by ECL-based assay

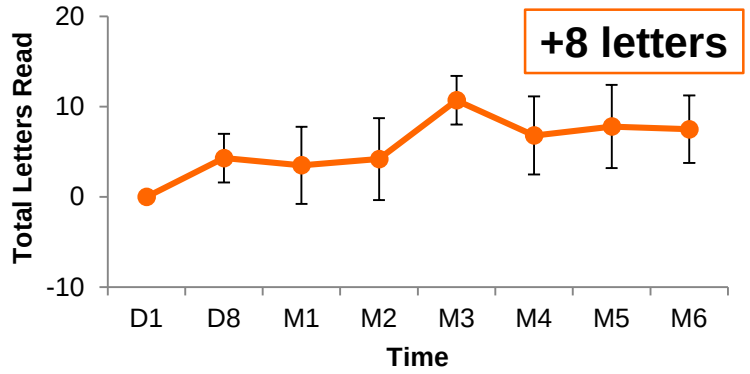


RGX-314 Phase I Trial: Mean Change in BCVA, CRT and Average Injections Over Six Months, by Cohort

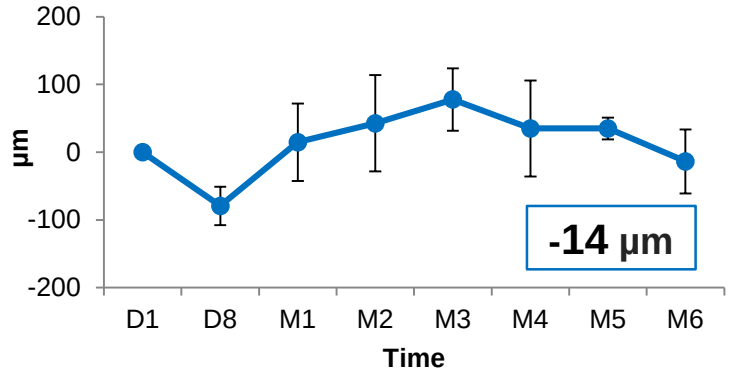
Best Corrected Visual Acuity (BCVA)

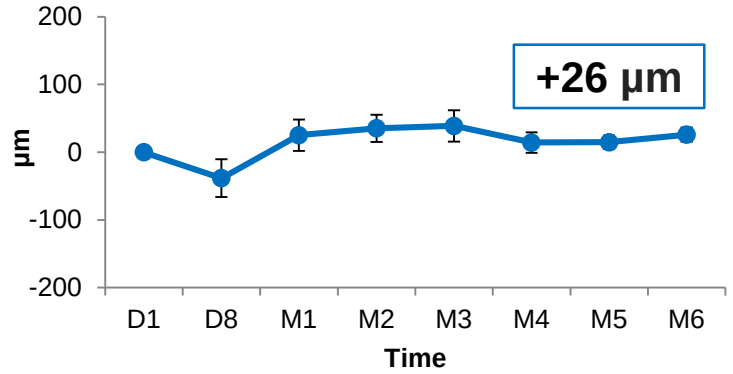


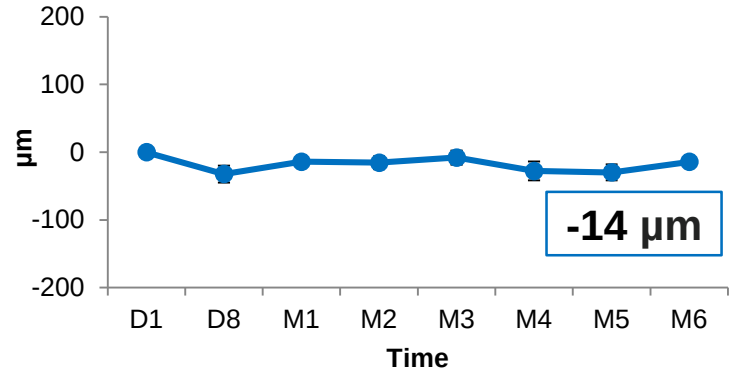




Central Retinal Thickness (CRT) on SD-OCT







Average Injections: 4.7	Average Injections: 3.8	Average Injections: 1.3
Cohort 1	Cohort 2	Cohort 3

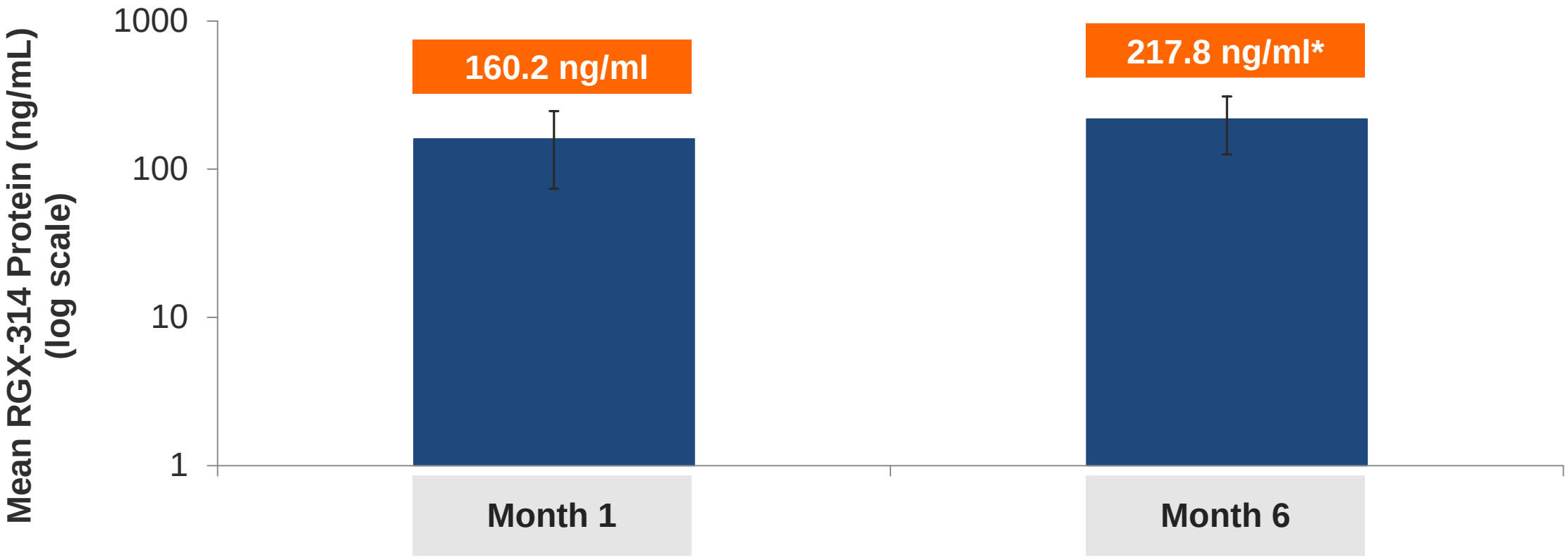
RGX-314 Phase I Trial: Summary of Interim Results Through Six Months

	Mean Aqueous RGX-314 Protein One Month Post-treatment	Mean # of Anti-VEGF Injections Through Six Months	Mean Change in CRT Through Six Months (range)	Mean Change in BCVA Through Six Months (range)
Cohort 1 $3x10^9$ GC/eye (N=6)	2.4 ng/ml	4.7 inj*	-14 µm** (-181 to +92 µm)	-2 letters** (-8 to +10 letters)
Cohort 2 $1x10^{10}$ GC/eye (N=6)	12.8 ng/ml	3.8 inj	+26 µm (-7 to +62 µm)	+7 letters (-4 to +15 letters)
Cohort 3 $6x10^{10}$ GC/eye (N=6)	**160.2 ng/ml**	**1.3 inj**	**-14 µm** (-27 to +7 µm)	**+8 letters** (0 to +21 letters)

* One subject in Cohort 1 discontinued from the study at four months with four injections and was imputed as requiring six injections through six months
** N=5; one subject in Cohort 1 discontinued from the study at four months

RGX-314 Phase I Trial: Sustained Protein Levels at Six Months

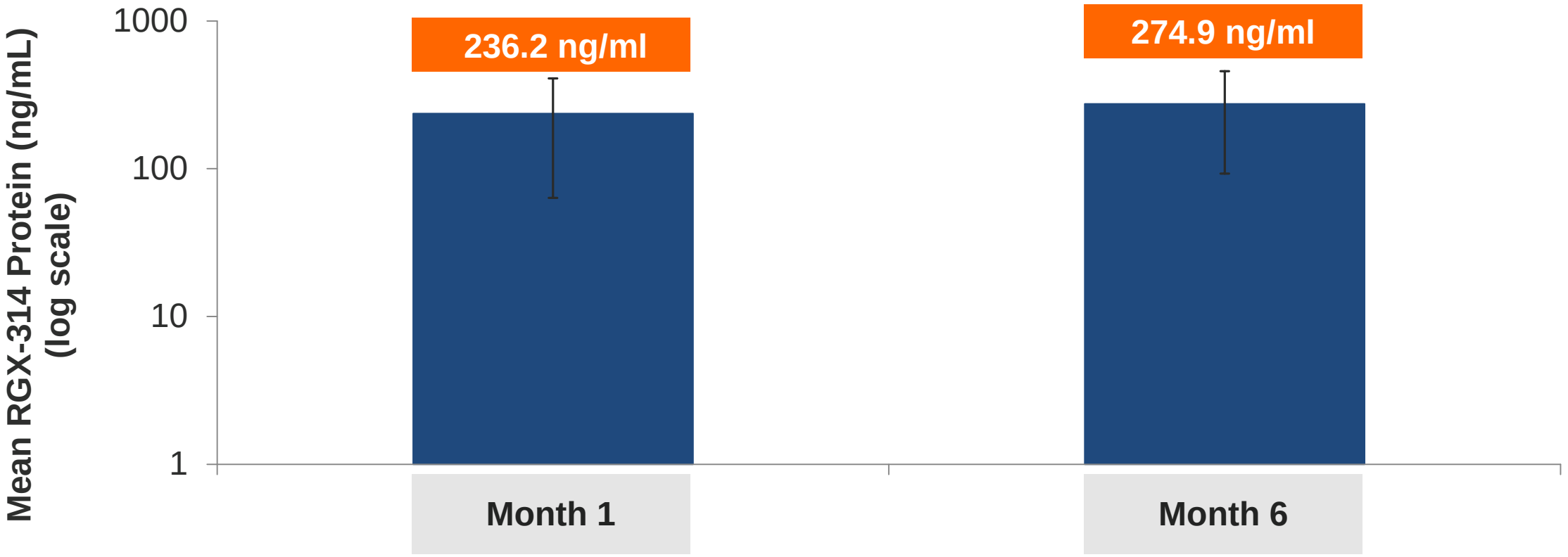
All Subjects (N=6) in Cohort 3



*One subject received an anti-VEGF rescue injection 1 month prior to sample.

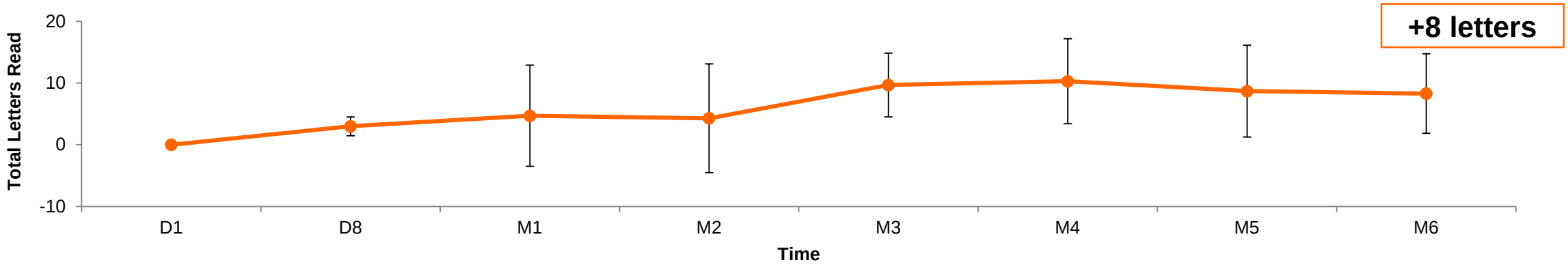
RGX-314 Phase I Trial: Sustained Protein Levels at Six Months

Subjects with No Rescue Injections (n=3) in Cohort 3

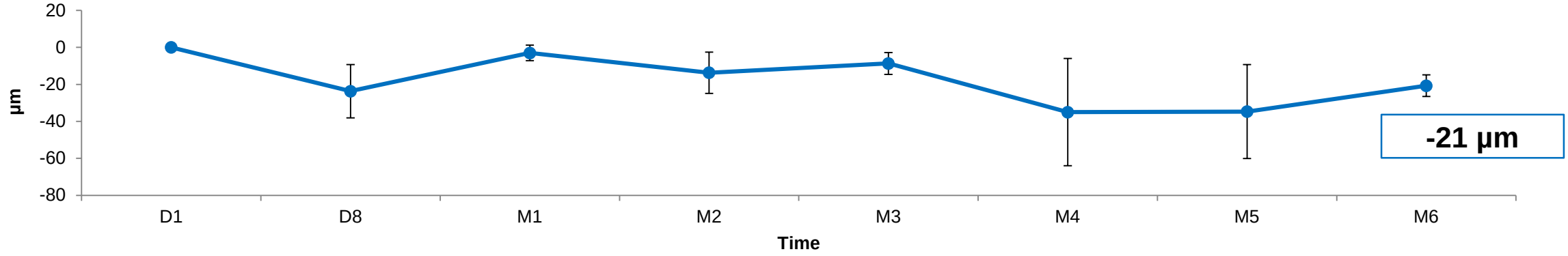


RGX-314 Phase I Trial: Mean Change in BCVA, CRT Over Six Months in Cohort 3 Subjects with No Rescue Injections

Best Corrected Visual Acuity (BCVA)



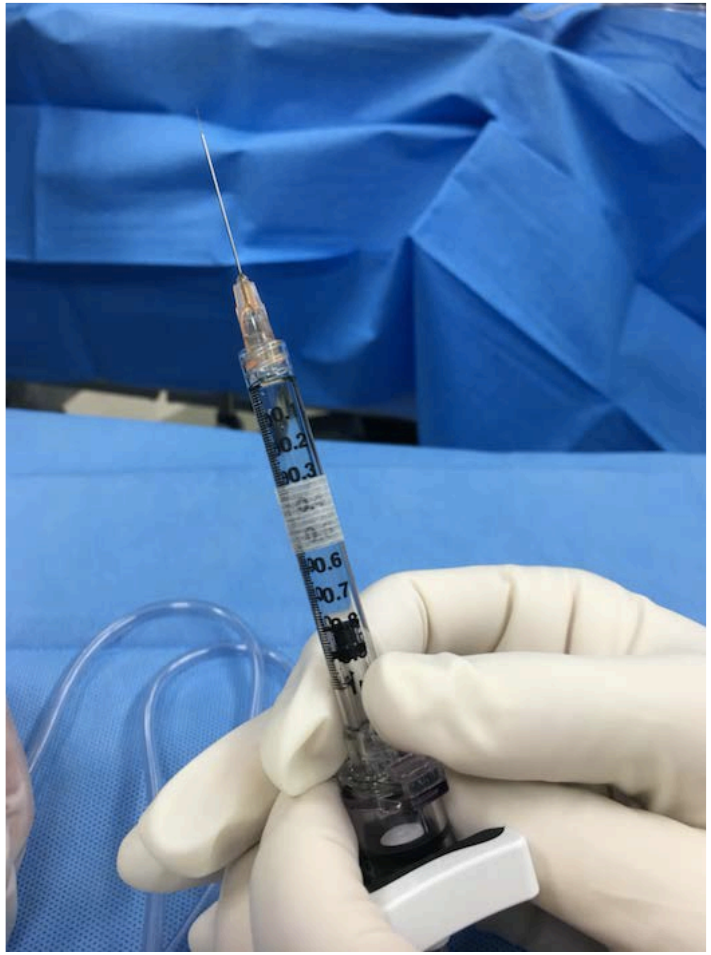
Central Retinal Thickness (CRT) on SD-OCT



Cohort 3 with No Rescue Injections (n=3)

RGX-314: Phase I Trial Interim Results at Six Months Conclusions

- RGX-314 was **well-tolerated** at all doses
- Dose-dependent **RGX-314 protein expression**
- Cohort 3: **sustained RGX-314 protein at six months** with **stability in vision and anatomy** despite **few to no injections**
- Cohort 4: a higher dose recently **completed dosing**
- **Gene therapy** for nAMD offers the potential to optimize outcomes while alleviating treatment burden



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- **Szilard Kiss, MD** (New York, NY)
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- **Darin Curtis, PharmD** (REGENXBIO)
- **Stephen Yoo, MD** (REGENXBIO)