Suprachoroidal Delivery of RGX-314 for Diabetic Retinopathy Without CI-DME: Results from the Phase II ALTITUDE™ Study

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Angiogenesis, Exudation and Degeneration

Disclosures

- Genentech - S, C
- Regeneron - S
- Allergan - S
- REGENXBIO - C

C: Consultant S: Speaker

Diabetic Retinopathy is a Global Public Health Problem

Diabetic Retinopathy (DR) is the Leading Cause of Blindness Among Working-Age Adults Globally[1]

- **Over 25 million patients are affected with DR in the US, Europe and Japan, including 10 million in the US alone**

Chronic, frequent treatment with anti-VEGF agents has been shown to improve DR severity and reduce risk of progression to vision threatening complications (VTCs) by > 70%[2]

- **Q8 weeks EYLEA® (aflibercept) and Q4 weeks LUCENTIS® (ranibizumab) are FDA approved for the treatment of DR without VTCs[3]**

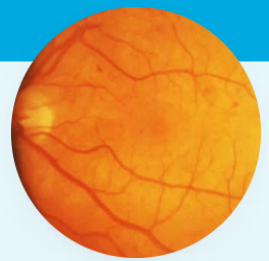
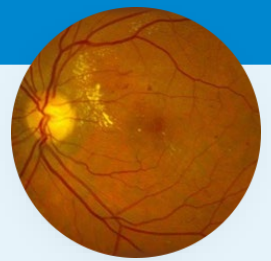
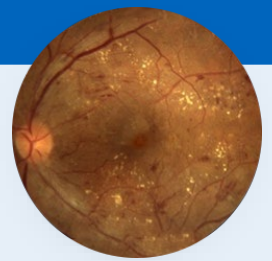
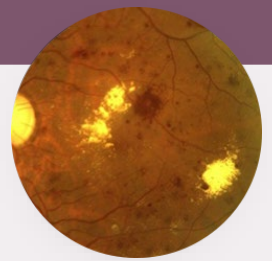
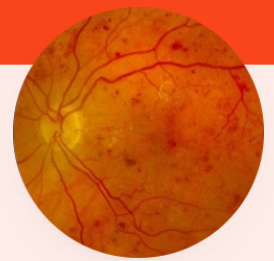
Majority of DR patients without VTCs are not treated with anti-VEGF in the real world due to the unsustainable treatment burden of frequent injections in the eye[4]

One time, in-office injection of gene therapy could potentially provide long-lasting improvement in DR severity and reduce risk of vision threatening complications

1. Lee, R., Wong, T.Y. & Sabanayagam, C. *Eye and Vis* 2015 2. Bakri, 2021. ASRS. 3. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. March 2021; Lucentis® (ranibizumab) Prescribing information. Genentech, Inc., March 2018. 4. Wykoff, CC, 2021. *Diabetes Care*. 5. PAT Survey, ASRS 2021.

A 2-step Improvement in Diabetic Retinopathy Severity Scale (DRSS) Has Been Accepted as a Pivotal Endpoint by the FDA for DR Clinical Trials[1]

▸ INCREASING RISK OF DEVELOPING VISION THREATENING COMPLICATIONS ▸

DRSS 35 Mild NPDR	***DRSS 43*** Moderate NPDR	***DRSS 47*** Moderately Severe NPDR	***DRSS 53*** Severe NPDR	***DRSS ≥ 60*** PDR
				
• Visual symptoms mostly absent • Small bulges in blood vessels and intraretinal hemorrhages	• May experience visual symptoms • Spotted leaking of blood	• May experience visual symptoms • Leaking of blood in retina, unevenly shaped veins	• May experience visual symptoms • Widespread leaking of blood, more unevenly shaped veins	• Visual symptoms are usually present • Growth of new fragile blood vessels, in some cases leading to bleeding in the retina and center of the eye

Example of 2-step improvement

DR disease severity is measured using the Diabetic Retinopathy Severity Scale [2]

DR, diabetic retinopathy. CI-DME can occur at any stage of severity.

1. Used in the approval of EYLEA® (aflibercept) and LUCENTIS® (ranibizumab) Source: AAO PPP 2019; 2. DRSS score categorizes severity of disease in DR. ETDRS report number 12. *Ophthalmology* 1991; Images: Bakri, 2021

RGX–314 for the Treatment of Diabetic Retinopathy (DR)

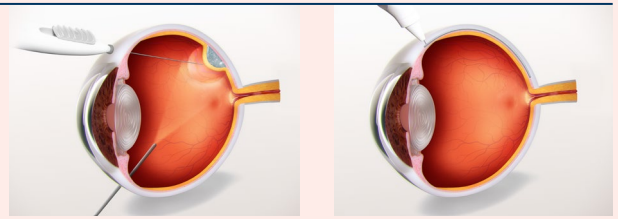
RGX–314 PRODUCT CANDIDATE

Vector: AAV8 | **Gene:** anti-VEGF fab

Route of administration:

Subretinal (nAMD) or

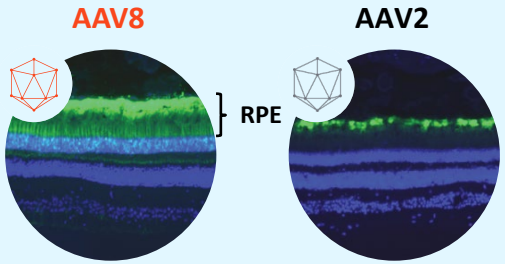
Suprachoroidal (nAMD/DR)



Mechanism of action:

Reducing leaky blood vessel formation by giving ocular cells the ability to produce an anti-VEGF fab

Improved AAV vector technology



More efficient gene delivery to the RPE[1]

+

Leveraging current standard of care in transgene

- FDA-approved mAbs and mAb fragments that inhibit VEGF are used for the prevention of DR complications
- **RGX–314 gene encodes an anti-VEGF mAb fragment (fab)**

=

RGX–314: AAV8 encoding anti–VEGF fab

Potential for long-term therapeutic anti-VEGF expression

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

AAV: Adeno-Associated Virus.

ALTITUDE™: RGX-314 Phase II Clinical Trial in Diabetic Retinopathy

Primary Objective

- Evaluate proportion of patients with ≥2 step improvement in severity on the Diabetic Retinopathy Severity Scale (DRSS) at one year

Secondary Objectives

- Safety and tolerability of RGX-314
- Development of DR-related ocular complications
- Need for additional standard of care interventions

Subjects: Up to 60 total

- 18 study sites across the United States

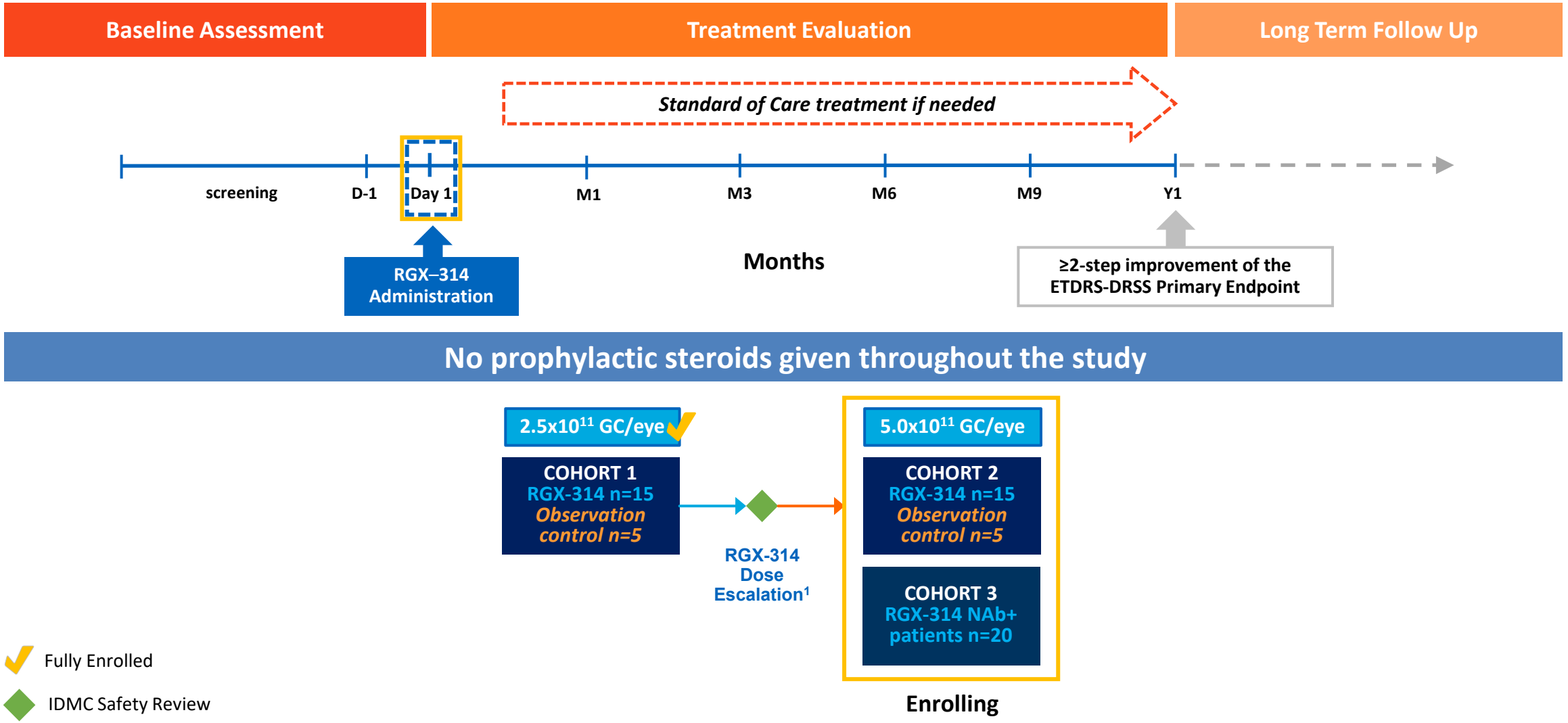
Route of Administration

- In-office SCS Microinjector™ delivers RGX-314 to the **suprachoroidal space**

Key Inclusion Criteria

- Male or female ≥ 25 to 89 years of age with DR secondary to diabetes mellitus Type 1 or Type 2
- **Moderately Severe NPDR, Severe NPDR, or Mild PDR (DRSS levels 47-61)**
- No active CI-DME, CST < 320 µm
- Vision of 20/40 or better (≥ 69 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) in the study eye
- No anti-VEGF injection(s) in prior 6 months

RGX-314 ALTITUDE™ Study Design



1. Dose escalation safety review to occur two weeks after final subject in each cohort has been dosed.
NAb+ = AAV8 neutralizing antibody positive. Y1= 48 weeks.

ALTITUDE Baseline Characteristics (Cohort 1)

	Variable	Observational Control (N=5)	RGX-314 (N=15)	Total (N=20)
BASELINE[1]	**Mean Age** (Years)	51.0	50.7	50.8
	Gender – Female	1 (20%)	9 (60%)	10 (50%)
	Hemoglobin A1c	6.4	8.2	7.8
	Baseline DRSS score			
	47 (Moderately Severe, NPDR)	5 (100%)	5 (33.3%)	10 (50.0%)
	53 (Severe, NPDR)		2 (13.3%)	2 (10.0%)
	61 (Mild, PDR)		7 (46.7%)	7 (35%)
	65[2] (Moderate, PDR)		1 (6.7%)	1 (5%)
	Screening BCVA (Snellen equivalents)	87.6 (20/20)	78.1 (20/32)	80.5 (20/25)
	Screening OCT CRT (µm)	259.2	259.5	259.5
	Lens Status – Phakic n (%)	4 (80%)	13 (86.7%)	17 (85%)
DISEASE HISTORY	**Study Eye with anti-VEGF Injections in the Past 36-months** n (%)	0	5 (33.3%)	5 (25%)
	Months Since DR Diagnosis[3] – Mean	31.9	27.8	28.8

1. Ocular variables refer to study eye only.
2. After randomization, central reading center DRSS was scored as Grade 65 on final masked adjudication.
3. Based on randomization date.

ALTITUDE Safety Summary: Cohort 1

- RGX–314 was **well-tolerated** (n=15)
  - 2 SAEs: not considered drug-related
    - Vitreous hemorrhage in an untreated *fellow eye*
    - Femur fracture
- **Common ocular TEAEs[1] in the study eye were not considered drug-related and were predominantly mild**:
  - Conjunctival hyperemia (3/15, 20%)
  - Conjunctival hemorrhage (2/15, 13%)
- One case of mild episcleritis reported 2-weeks post-dosing and resolved with topical corticosteroids
- **No intraocular inflammation** observed
  - No prophylactic corticosteroids administered
- **Stable BCVA**

	Observational Control (N=5)	Cohort 1 $2.5x10^{11}$ GC/eye (N=15)
Mean change in BCVA at M6	**-2.0 letters**	**+0.3 letters**

Data cut: January 18, 2022

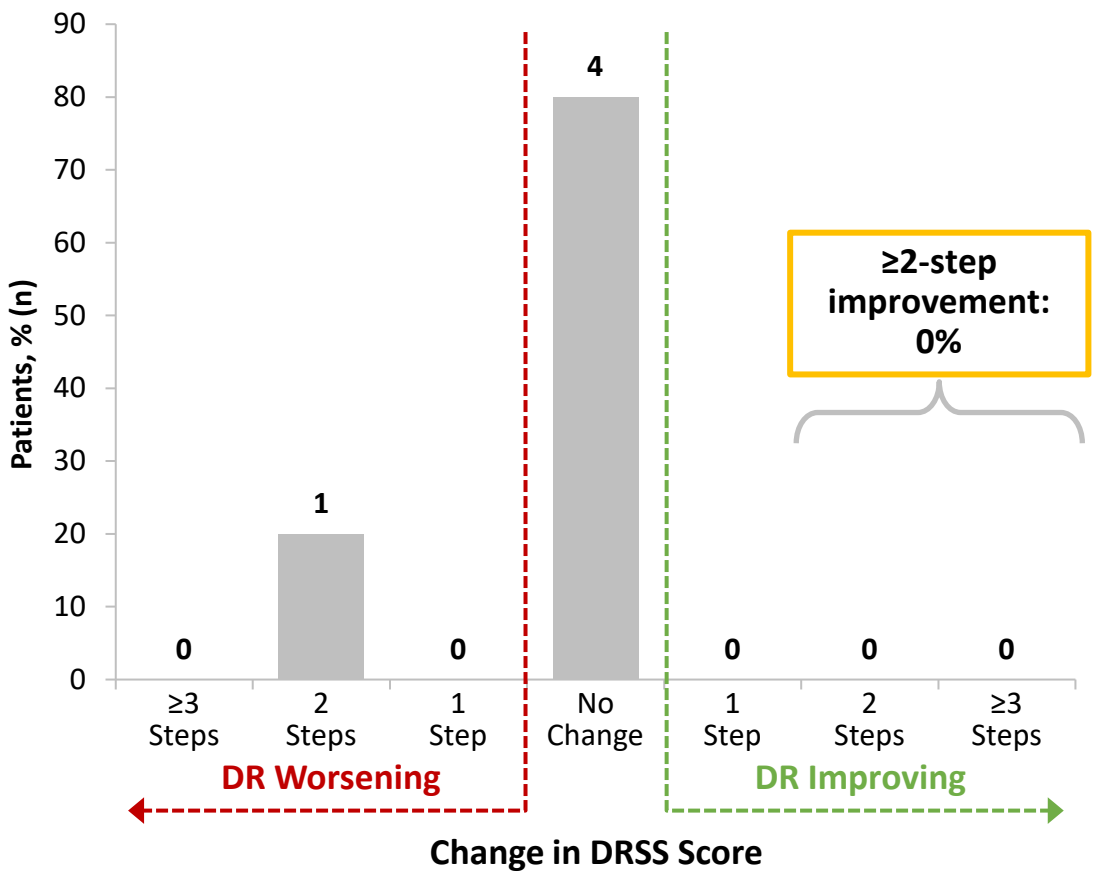
1. Ocular TEAEs through 6-month visit, with common ocular TEAEs defined as ≥ 10% of RGX-314 treated study eyes.

SAE: Serious Adverse Event; TEAE: Treatment Emergent Adverse Event

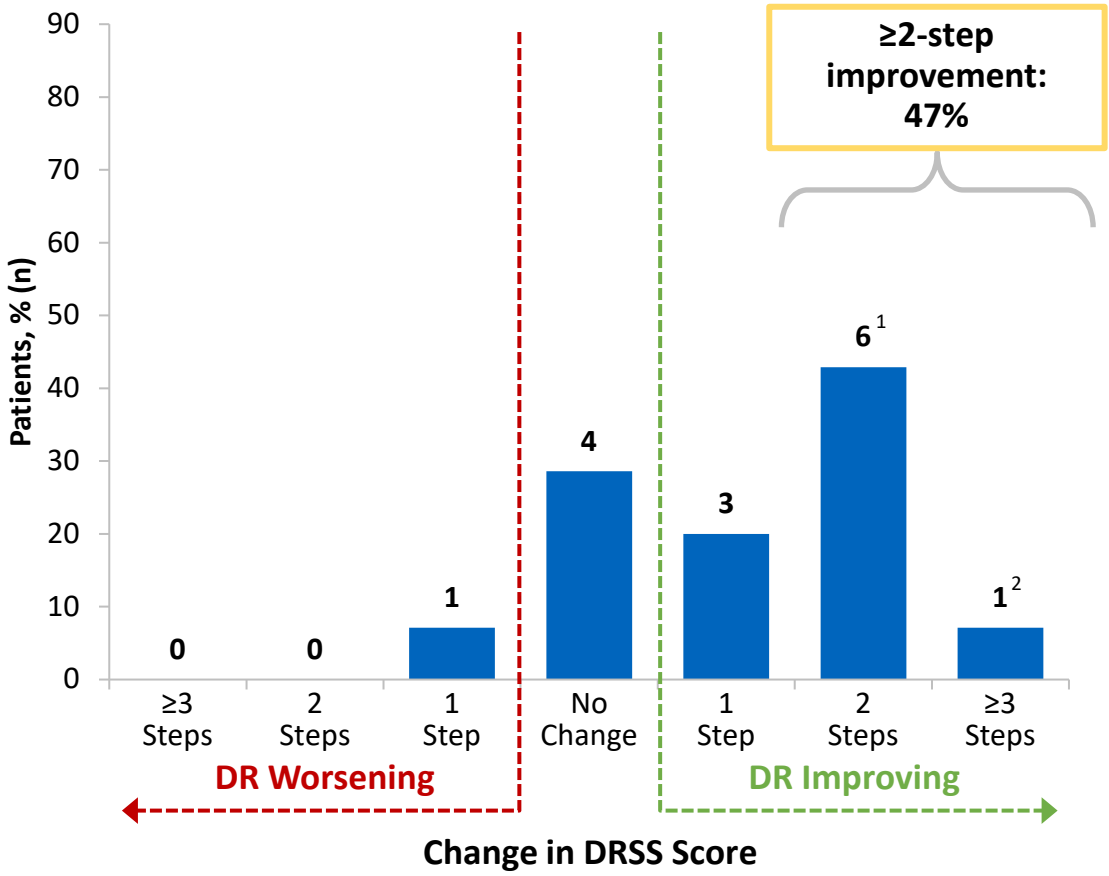
Cohort 1: Change in DRSS at Month 6

47% of RGX-314 Treated Patients Achieved a ≥2-Step Improvement in Disease Severity

Observational Control (n=5)



RGX-314 (n=15)



A **2-step improvement** in DRSS has been accepted as a **pivotal endpoint** by the **FDA** for **DR clinical trials**[3]

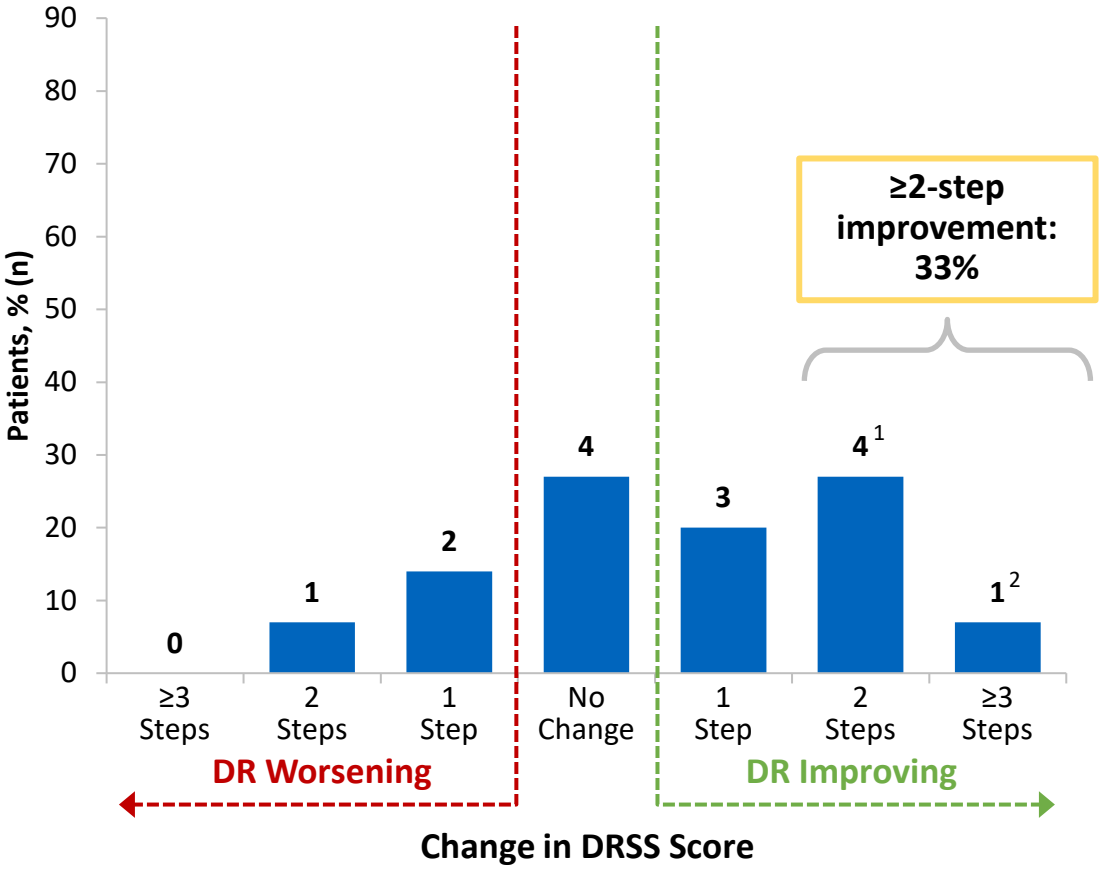
Data cut: January 18, 2022

1. One study eye (DRSS 61 at baseline) received a single Lucentis injection 8 days after RGX-314 dosing for trace vitreous hemorrhage, which was 10 weeks prior to their 3 month visit when DRSS was assessed.
2. One patient had a 4-step improvement.
3. Used in the approval of EYLEA® (aflibercept) and LUCENTIS® (ranibizumab) Source: AAO PPP 2019

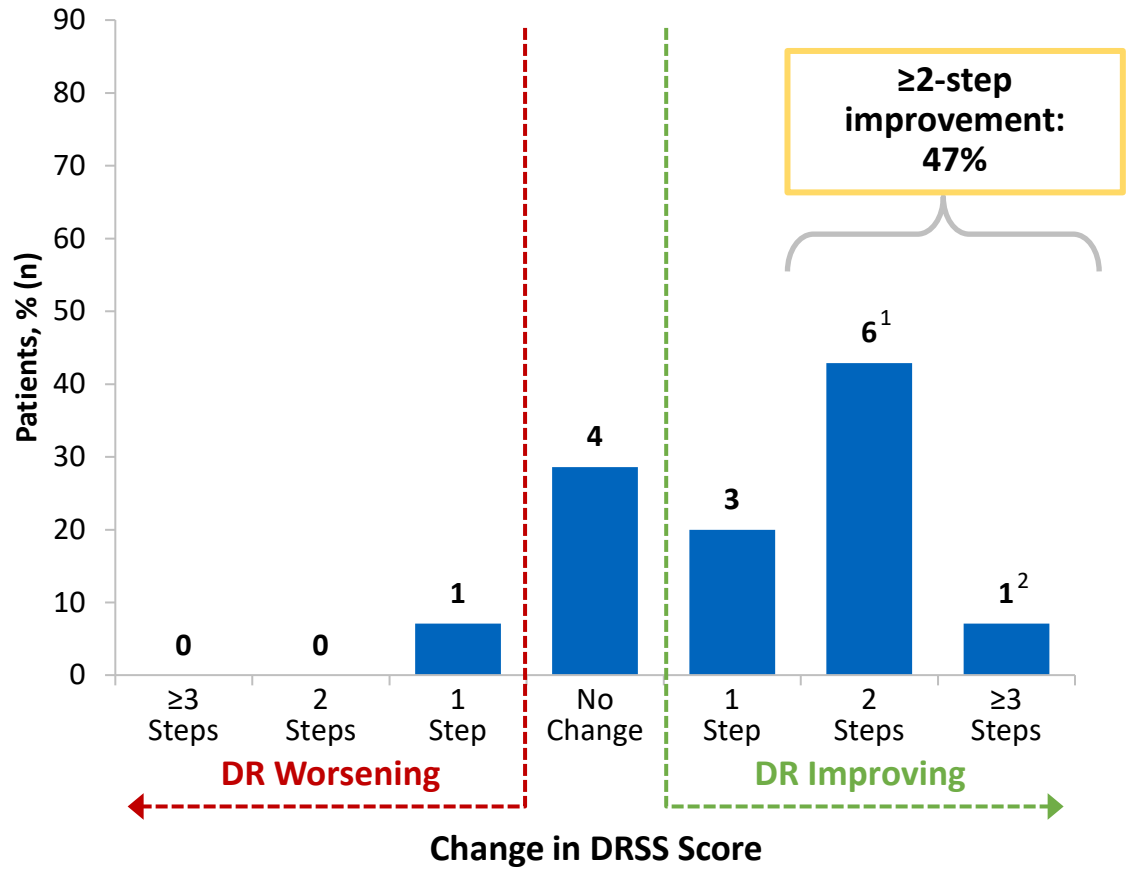
Cohort 1: Change in DRSS at Months 3 and 6

Patients Treated with RGX-314 Demonstrated Improvement in Disease Severity Over Time

RGX-314 (n=15) at 3 months



RGX-314 (n=15) at 6 months



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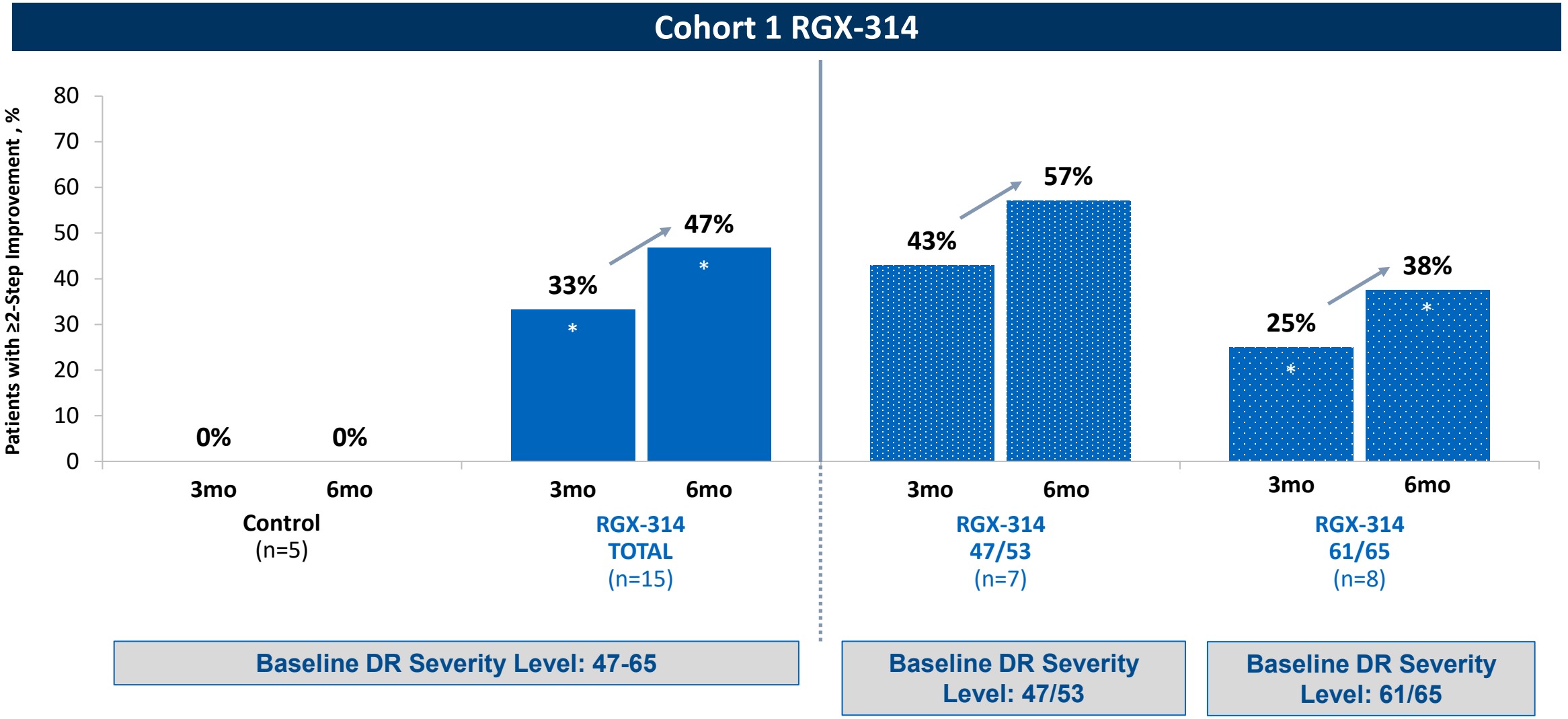
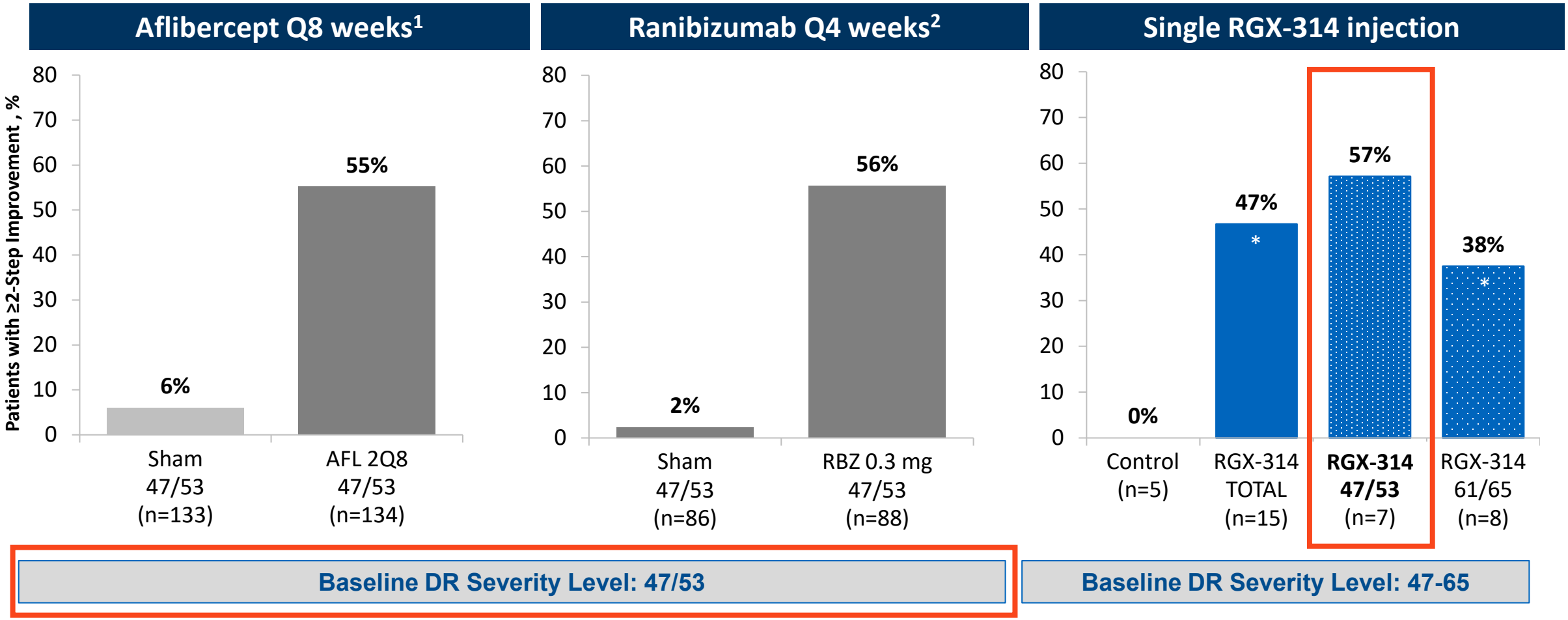
Patients with ≥2 Step Improvement in Disease Severity at Months 3 and 6



Data cut: January 18, 2022.

*One patient had a 4-step improvement. Another patient received a single Lucentis injection in the study eye (DRSS 61 at baseline) 8 days after RGX-314 dosing for trace vitreous hemorrhage, which was 10 weeks prior to their 3 month visit when DRSS was assessed.

How Do ALTITUDE Cohort 1 DRSS Outcomes at 6 Months Compare to Frequent Injections of FDA-Approved Anti-VEGF?



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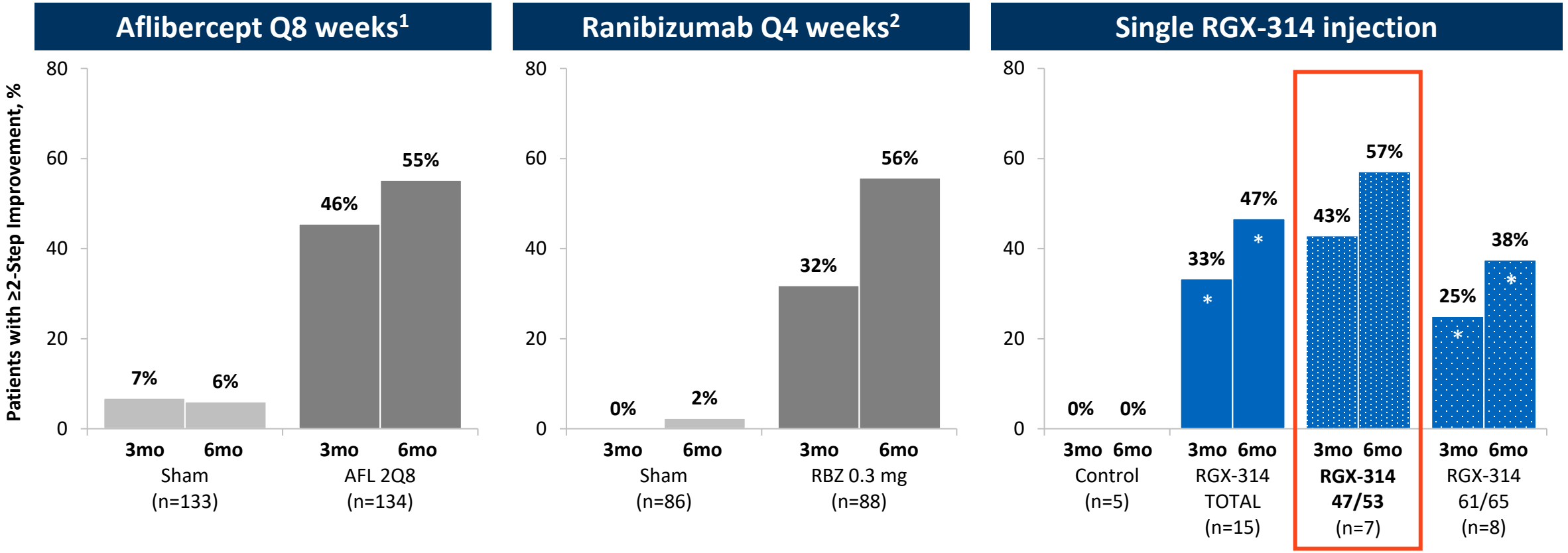
1. Patients initially received 5 Q4 weeks loading doses followed thereafter by Q8 weeks dosing, per U.S. label instructions; EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. March 2021.
2. Patients received Q4 weeks dosing of ranibizumab (RBZ), per U.S. label instructions; Wykoff CC et al. *Ophthalmology Retina*. 2018 DOI: (10.1016/j.oret.2018.06.005).

How Do DRSS Outcomes After a Single Injection of RGX-314 Compare to FDA-Approved Anti-VEGF Dosing Regimens?



Baseline DR Severity Level: 47/53

Baseline DR Severity Level: 47-65

Data cut: January 18, 2022

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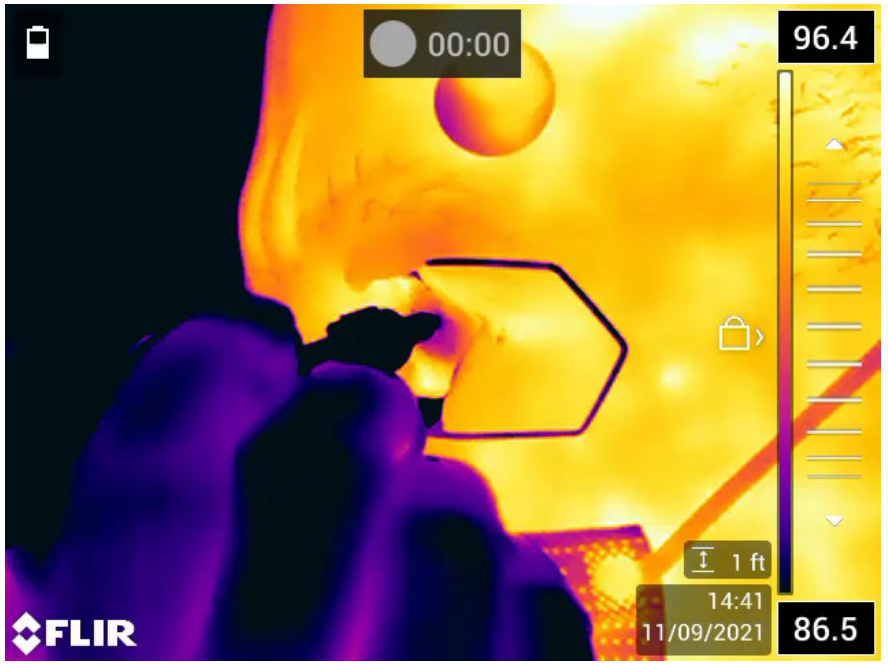
Summary of Results from the Phase II ALTITUDE™ DR Study

- Suprachoroidal RGX-314 continues to be **well-tolerated** in Cohort 1 ($2.5x10^{11}$ GC/eye; n=15)
- **No intraocular inflammation observed over 6 months**
  - No prophylactic corticosteroids administered
- With a **single** injection of RGX-314, **patients demonstrate clinically meaningful improvements in disease severity over time**
  - 33% achieved a ≥2 step improvement at 3 months
  - **47% achieved a ≥2 step improvement at 6 months**



Video: M. Klufas

A one time, in-office injection of gene therapy could potentially provide long-lasting improvement in DR severity and reduce risk of vision threatening complications

ALTITUDE study is currently enrolling Dose level 2 ($5.0x10^{11}$ GC/eye)
in Cohorts 2 and 3: NAb- and NAb+ patients

Data cut: January 18, 2022