Suprachoroidal Delivery of RGX-314 for Diabetic Retinopathy Without CI-DME: The Phase II ALTITUDE® Study

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Retina Society

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Disclosures

AbbVie/Allergan: C
AGTC: G
Alcon Laboratories, Inc: C, G
Aldeyra: G
Alimera Sciences: C
Apellis: C
Bausch & Lomb: C
Beaver-Visitec International, Inc.: C
BMC: C
Coherus Biosciences: C
DORC: C
Guidepoint: C
Gyroscope/Orbit Biomedical: C, G
Heidelberg Engineering – G
Iveric Bio – C
National Eye Institute: G
Ocugen Inc.: C
OcuTerra: C
REGENXBIO: C, G
Roche/Genentech: C, G
Vindico Medical Education: C

C: Consultant/Advisor; G: Grant Support; O: Equity / Stock Owner; P: Patents / Royalty

Diabetic Retinopathy is a Global Public Health Problem

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

- **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%[b]

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

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[d]

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

a. Lee, R., Wong, T.Y. & Sabanayagam, C. *Eye and Vis* 2015. b. Bakri, 2021. ASRS. c. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. March 2021; Lucentis® (ranibizumab) Prescribing information. Genentech, Inc., March 2018. d. Wykoff, CC, 2021. *Diabetes Care*.

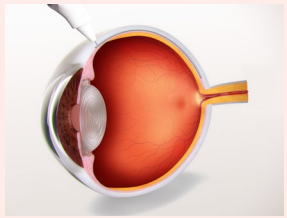
RGX–314 for the Treatment of Diabetic Retinopathy (DR)

RGX–314 PRODUCT CANDIDATE

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

Route of administration:

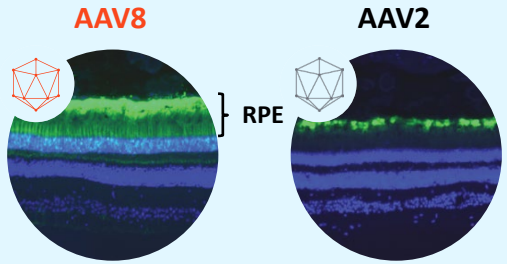
Suprachoroidal



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[a]

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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

a. 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: 60 patients enrolled

- 50 RGX-314; 10 observation control
- 21 study sites across the United States

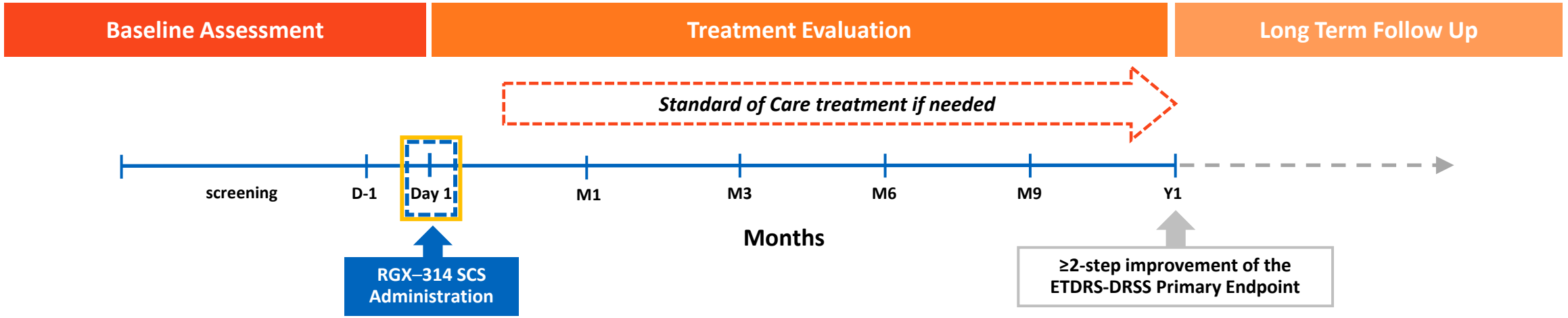
Route of Administration

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

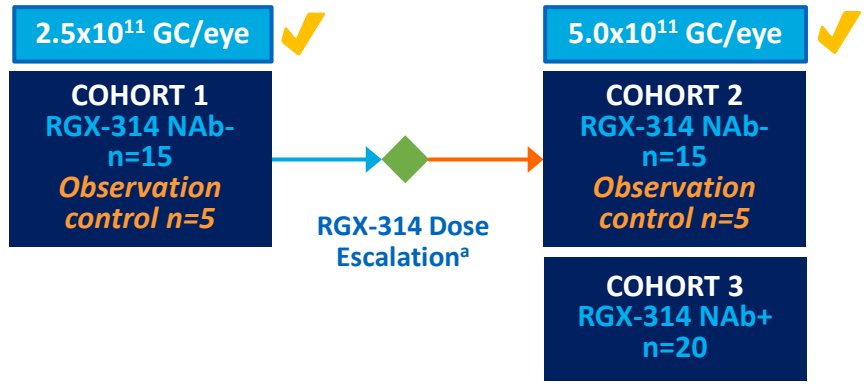
Key Inclusion Criteria

- 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 (N=60)



No prophylactic steroids given throughout the study



✓ Fully Enrolled

◆ IDMC Safety Review

a. Dose escalation safety review to occur two weeks after final subject in each cohort has been dosed.

SCS: Suprachoroidal Space; NAb+ = AAV8 neutralizing antibody positive; NAb- = AAV8 neutralizing antibody negative/low; Y1 = 48 weeks.

ALTITUDE® Baseline Characteristics (Cohort 1–3)

	Variable	Observational Control (N=10)	Cohort 1 (N=15)	Cohort 2 (N=15)	Cohort 3 (N=20)	Total (N=60)
BASELINE[a]	**Mean Age** (Years)	52.5	50.7	58.1	60.1	56.0
	Gender – Female	1 (10.0%)	9 (60.0%)	7 (46.7%)	8 (40.0%)	25 (41.7%)
	Hemoglobin A1c	7.7	8.2	8.5	8.2	8.2
	DR Category at Baseline					
	DRSS 47 (Moderately Severe NPDR)	8 (80.0%)	4 (26.7%)[b]	9 (60.0%)	12 (60.0%)	33 (55.0%)
	DRSS 53 (Severe NPDR)	0	2 (13.3%)	1 (6.7%)	2 (10.0%)	5 (8.3%)
	DRSS 61 (Mild PDR)	2 (20.0%)	8 (53.3%)[b]	5 (33.3%)	6 (30.0%)	21 (35.0%)
	DRSS 65 (Moderate PDR)	0	1 (6.7%)[c]	0	0	1 (1.7%)
	Screening BCVA (Snellen equivalents)	84.5	78.1	82.1	81.3	81.3
	Screening OCT CRT (µm)	275.4	259.5	272.4	274.4	270.4
	Lens Status – Phakic n (%)	9 (90.0%)	13 (86.7%)	10 (66.7%)	13 (65.0%)	45 (75.0%)
DISEASE HISTORY	**Study Eye with anti-VEGF Injections in the Past 36-months n** (%)	1 (10.0%)	5 (33.3%)	0	0	6 (10.0%)
	Months Since DR Diagnosis[d] – Mean	23.6	27.8	26.0	22.4[e]	24.9

a. Ocular variables refer to study eye only.
b. During an interim central reading center masked adjudication, 1 patient had baseline DRSS updated from Grade 47 to Grade 61 since prior interim data release.
c. After randomization, central reading center DRSS was scored as Grade 65 on masked adjudication.
d. Calculation based on randomization date.
e. One patient is missing date of DR diagnosis and not included.

ALTITUDE® Safety Summary

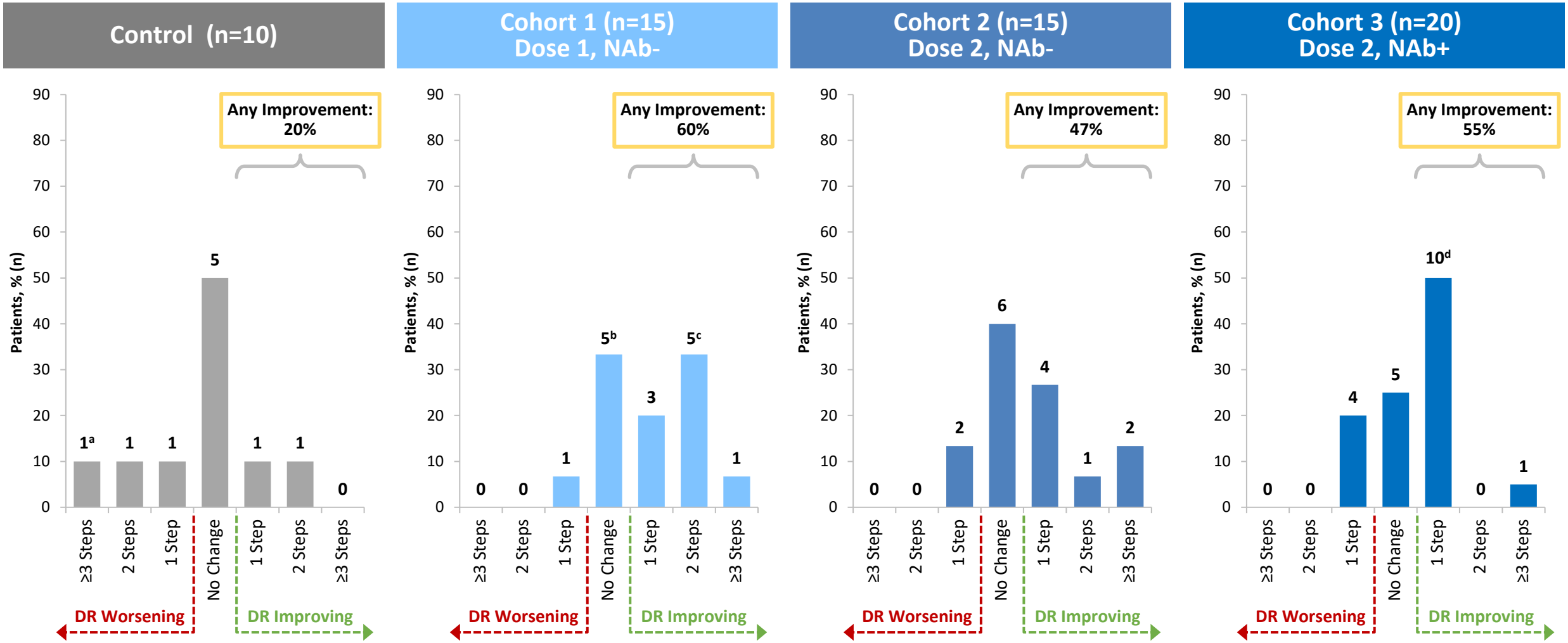
- **RGX–314 was well-tolerated in Cohorts 1–3 (n=50)**
  - 5 SAEs: None considered drug-related
  - No cases of chorioretinal vasculitis or occlusion, or hypotony were observed

Cohorts 1 to 3: Common Ocular TEAEs[a] and Intraocular Inflammation in the Study Eye through 6 Months	Cohort 1 Dose 1 NAb- (N=15)	Cohort 2 Dose 2 NAb- (N=15)	Cohort 3 Dose 2 NAb+ (N=20)	Total (N=50)
Conjunctival hyperemia	4 (26.7%)	5 (33.3%)	4 (20.0%)	13 (26.0%)
Conjunctival hemorrhage	3 (20.0%)	2 (13.3%)	1 (5.0%)	6 (12.0%)
Episcleritis[b]	1 (6.7%)	1 (6.7%)	4 (20.0%)	6 (12.0%)
Intraocular Inflammation[c]	0 (0.0%)	3 (20.0%)	0 (0.0%)	3 (6.0%)
		No meaningful differences based on **baseline AAV8 NAbs**		

- **Stable BCVA through 6 Months in Cohorts 1-3 (n=50)**

Data cut: October 17, 2022.
a. Common TEAEs include AEs for total group ≥10% with onset up to 6m visit.
b. All cases were mild (grade 1) and are resolved or resolving on topical corticosteroids.
c. All cases were mild (range +0.5 to +1) and most presented 2-6 weeks post injection, predominantly as anterior cells on slit lamp examination. Resolved on topical corticosteroids.
SAE: Serious Adverse Event; TEAE: Treatment Emergent Adverse Event.

Change in DRSS at Month 6



Data cut: October 17, 2022.

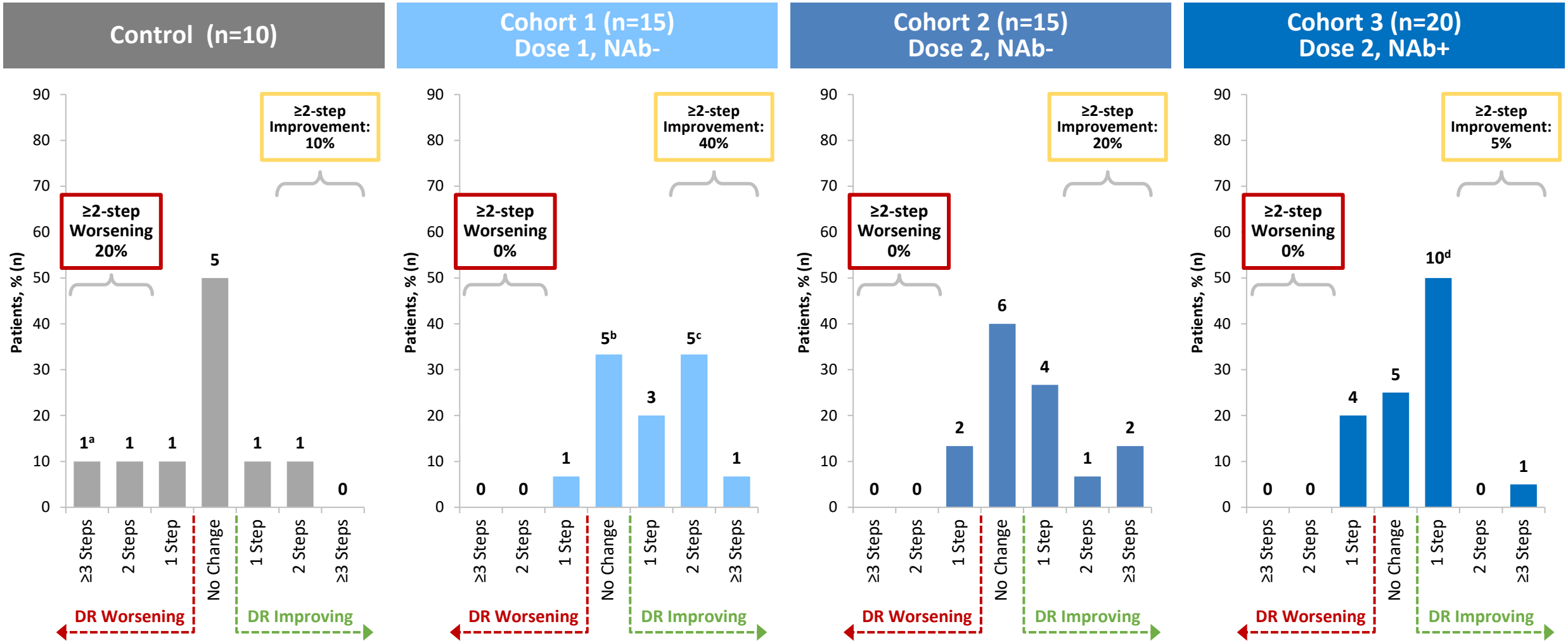
a. One observation control patient received two Lucentis injections in the study eye for vitreous hemorrhage (4-step worsening to DRSS 71 [severe PDR] at 6 months).

b. During an interim central reading center masked adjudication, 1 patient's DRSS grades at baseline and 6 months were updated from Grade 47 and Grade 35, respectively, to Grade 61 since prior interim data release.

c. One 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 22 weeks prior to their 6 month visit when DRSS was assessed.

d. One patient missed their 6-month visit, so their 3-month results were used.

Change in DRSS at Month 6



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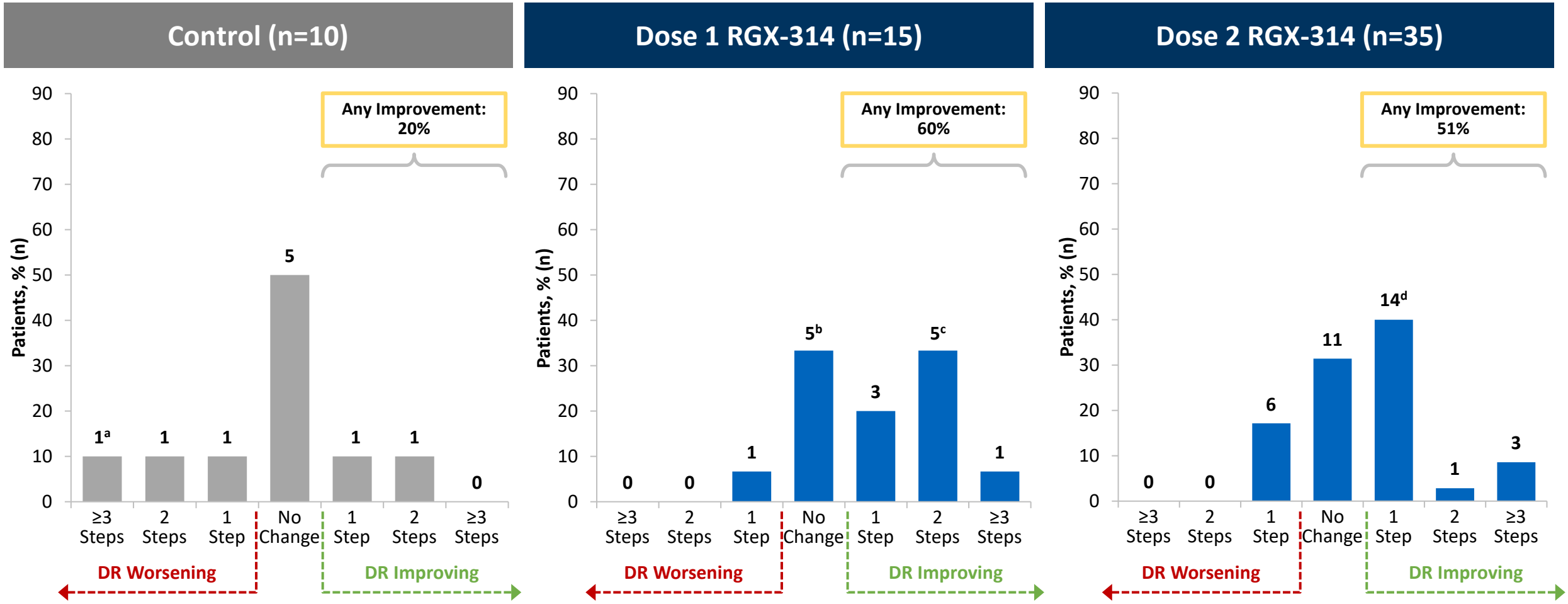
Change in DRSS at Month 6 by Dose



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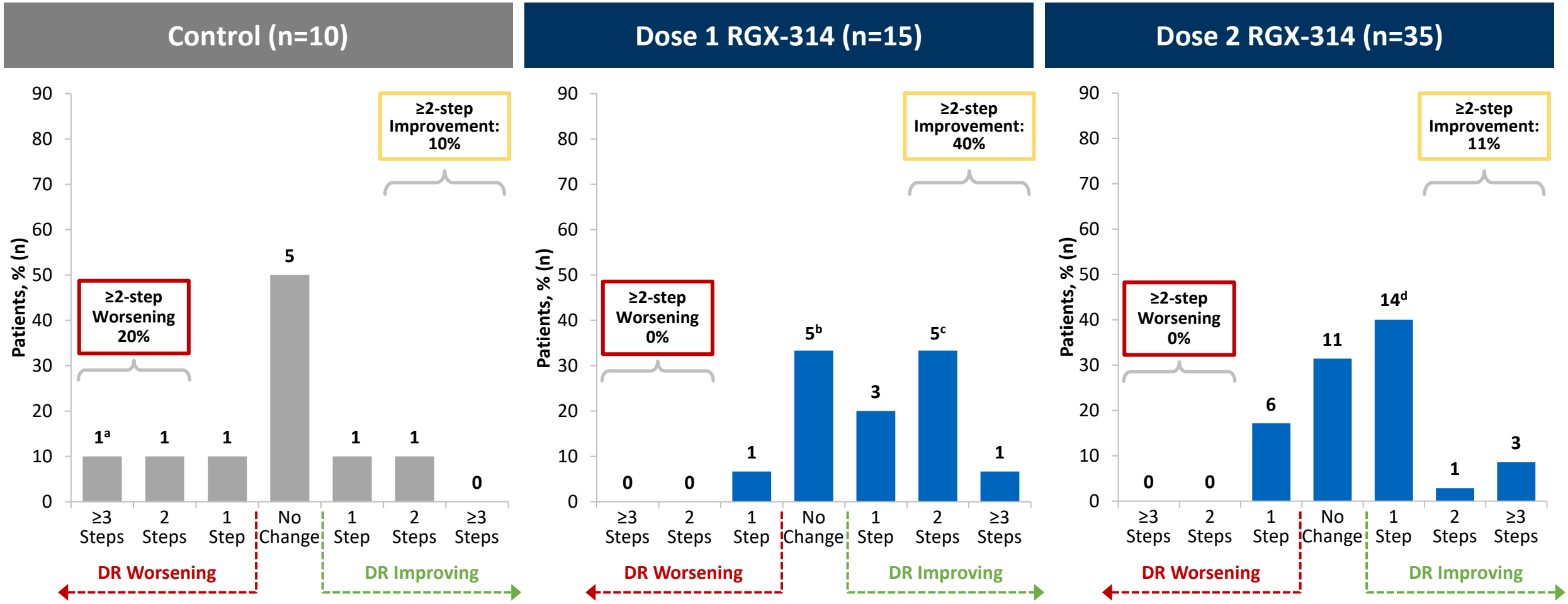
Change in DRSS at Month 6 by Dose



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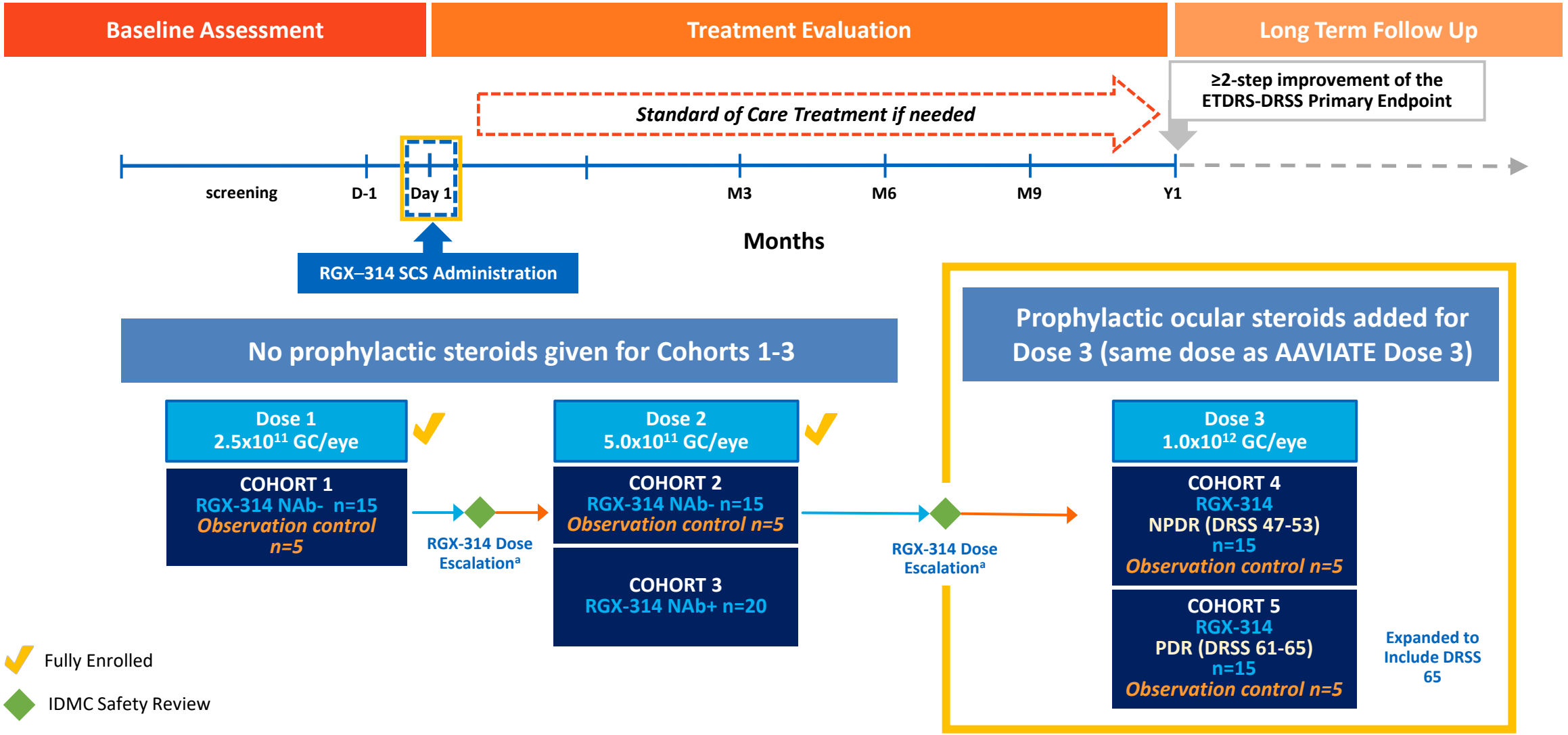
d. One patient missed their 6-month visit, so their 3-month results were used.

RGX-314 ALTITUDE® Study Design with Addition of Dose Level 3 (N=100)

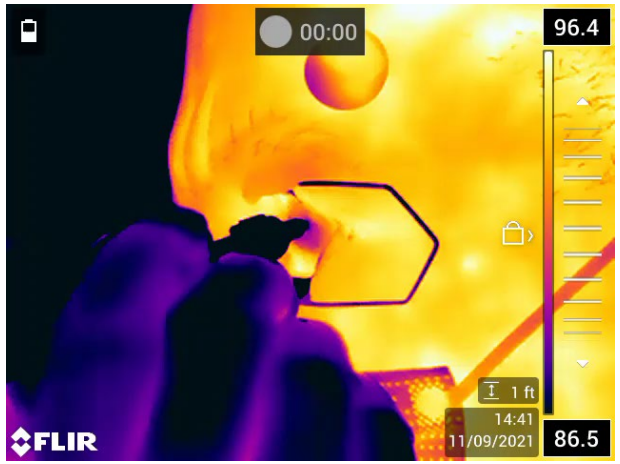


a. Dose escalation safety review to occur two weeks after final subject in each cohort has been dosed.

SCS: Suprachoroidal Space; NAb+ = AAV8 neutralizing antibody positive; NAb- = AAV8 neutralizing antibody negative/low; Y1 = 48 weeks; NPDR: Non-proliferative Diabetic Retinopathy; PDR: Proliferative Diabetic Retinopathy

Summary of 6 Month Results from the Phase II ALTITUDE DR Study

- Suprachoroidal RGX-314 continues to be **well-tolerated in Cohorts 1-3 (Dose 1: 2.5x10^{11} GC/eye; n=15 and Dose 2: 5.0x10^{11} GC/eye; n=35)**
- **Safety**
  - A few cases of mild intraocular inflammation were observed; resolved with topical corticosteroids
    - No prophylactic corticosteroids administered
  - No meaningful differences in patient outcomes with and without baseline AAV8 NAbs
- **Efficacy**
  - With a **single** injection of RGX-314 at Dose 1 & 2, **patients demonstrate clinically meaningful improvements in disease severity and less disease worsening**
    - 20% (D1: 40%; D2: 11%) achieved a ≥2-step improvement vs. 10% in control
    - 54% (D1: 60%; D2: 51%) achieved any DRSS improvement vs. 20% in control
    - 0% (D1: 0%; D2: 0%) worsened ≥2 steps vs. 20% in control



Video: M. Klufas

A one time, in-office injection of RGX-314 gene therapy could potentially provide long-lasting improvement in DR severity and reduce risk of vision threatening complications

ALTITUDE is currently enrolling a new Dose 3[a] (1x10^{12} GC/eye) with short-course, ocular steroids following RGX-314; new Cohorts 4 and 5 stratified by DRSS levels (NPDR, PDR)

Data cut: October 17, 2022.

a. ALTITUDE Dose 3 (1x10^{12} GC/eye) is the same dose as AAVIATE Dose 3.