Two Year Results from the Subretinal RGX-314 Gene Therapy Phase 1/2a Study for the Treatment of Neovascular AMD, and an Update on Suprachoroidal Trials

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AAO Retina Subspecialty Day

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Disclosures:

Consultant for: Adverum, Alcon, Alimera, Allergan, Amgen, Apellis, Asclepix, Bausch+Lomb, Clearside, Eyepoint, Genentech, Helio Vision, Notal Vision, Novartis, Ocular Therapeutix, Outlook, Pr3vent, REGENXBIO, Replenish, ReVana, Santen, Tenpoint Therapeutics, Visionary Ventures, InFocus Capital Partners.

Equity in: Adverum, Alcon, Alderya, Eyepoint, Iveric, Kodiak, Novartis, Regeneron, Replenish, ReVana, Verana Health, Visionary Ventures, InFocus Capital Partners.

RGX–314 for Treatment of Neovascular Age-related Macular Degeneration (nAMD) and Diabetic Retinopathy (DR)

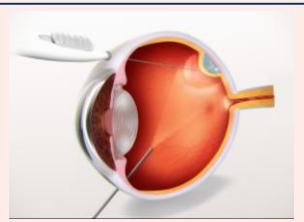
RGX–314 PRODUCT CANDIDATE

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

Route of administration:

Subretinal (nAMD) or

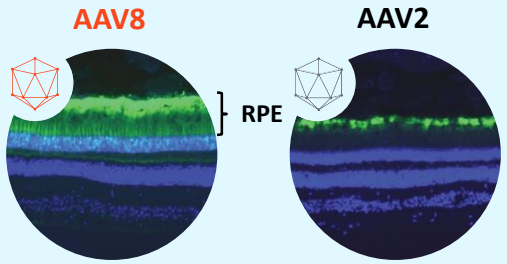
Suprachoroidal (nAMD/DR)



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 the current standard of care for treatment of nAMD, and are used for the prevention of DR complications
- **RGX–314 gene encodes an anti-VEGF mAb fragment (fab)**

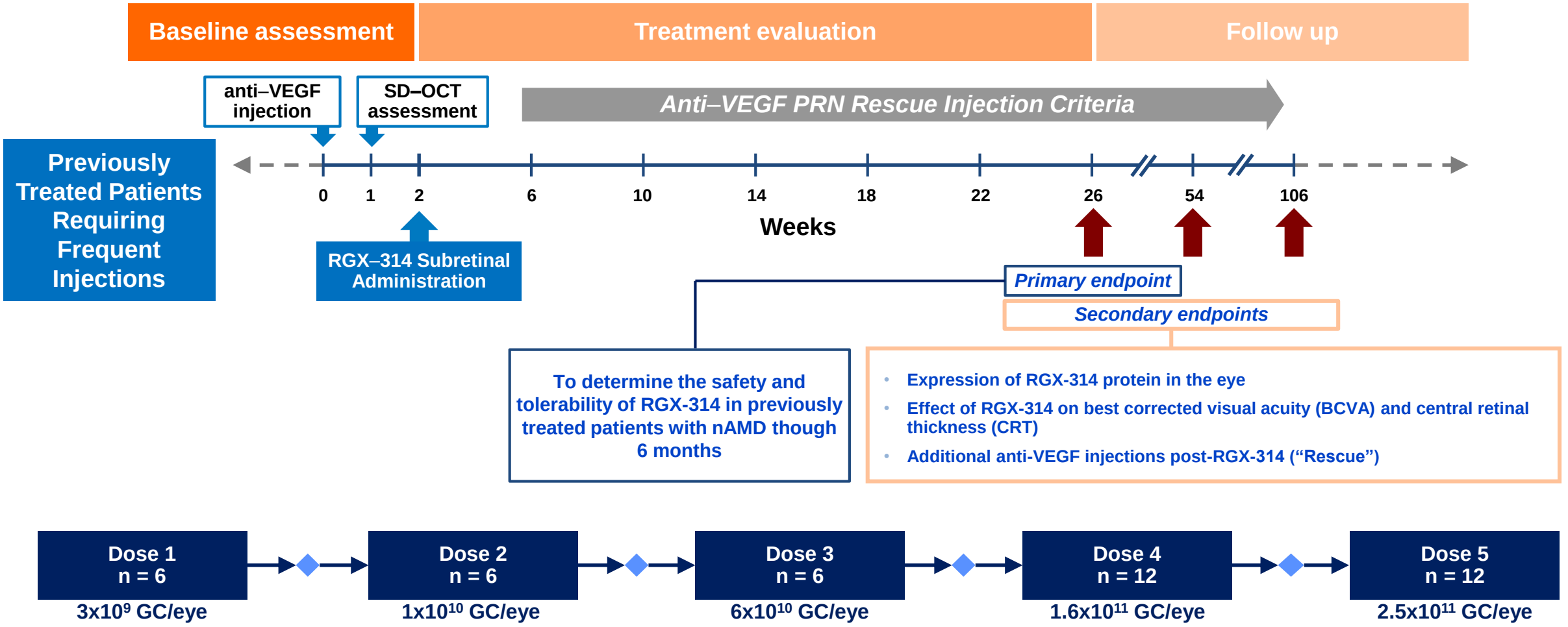
=

RGX–314: AAV8 encoding anti–VEGF fab

Potential for long-term therapeutic anti-VEGF expression

1. Vandenberghe et al. 2011 Science Translational Medicine

RGX-314 Phase I/IIa nAMD Study is Complete



◆ Safety review: Dose escalation safety review to occur four weeks after final patient in each cohort has been dosed

RGX-314 Phase I/IIa nAMD: Overall Safety

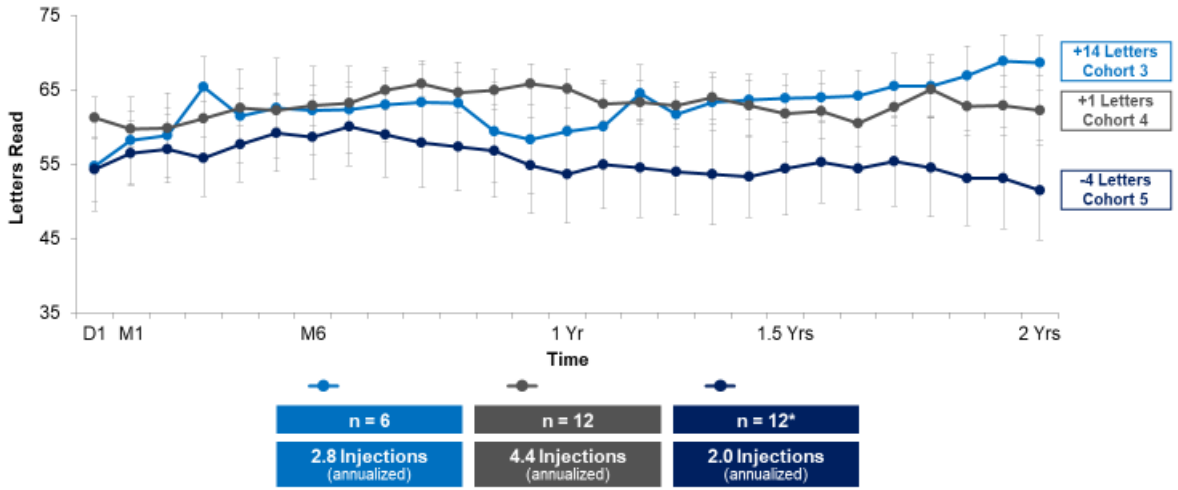
- **RGX–314 continues to be generally well–tolerated across all doses (n=42)**
- 20 SAEs were reported in 13 patients[1]; one possibly drug-related SAE reported in a patient in Cohort 5[2]
- Common ocular AEs[3] in the study eye included:
  - Retinal pigmentary changes[4] (69% of all patients; 87% of patients in Cohorts 3-5) – 62% mild, 2 severe (Cohort 5)[5]
  - Post-operative conjunctival hemorrhage (69% of patients) – 100% mild, majority resolved within days to weeks
  - Post-operative inflammation[6] (36% of patients) – resolved within days to weeks, 100% mild
  - Retinal hemorrhage (26% of patients) – an anticipated event in the severe nAMD population, 91% mild
  - Post-operative visual acuity reduction (17% of patients) – majority resolved within days to weeks, 100% mild
  - Eye irritation (17% of patients – 57% mild) and eye pain (17% of patients – 86% mild)
- ***No reports of clinically-determined immune responses, drug-related ocular inflammation, or post-surgical inflammation beyond what is expected following routine vitrectomy***

Data cut: September 13, 2021

1. Includes two deaths unrelated to RGX-314.
2. Significant decrease in vision.
3. Common ocular AEs defined by ≥ 15% of patients.
4. Retinal pigmentary changes observed were hypo and hyper pigmentation on imaging occurring in the bleb area or inferior retina.
5. The two severe cases occurred at the highest dose after receiving a superior bleb. These patients developed pigmentary changes peripherally, and in the macula, and had a decrease in vision.
6. Postoperative inflammation includes AC cells, flare, or inflammation.

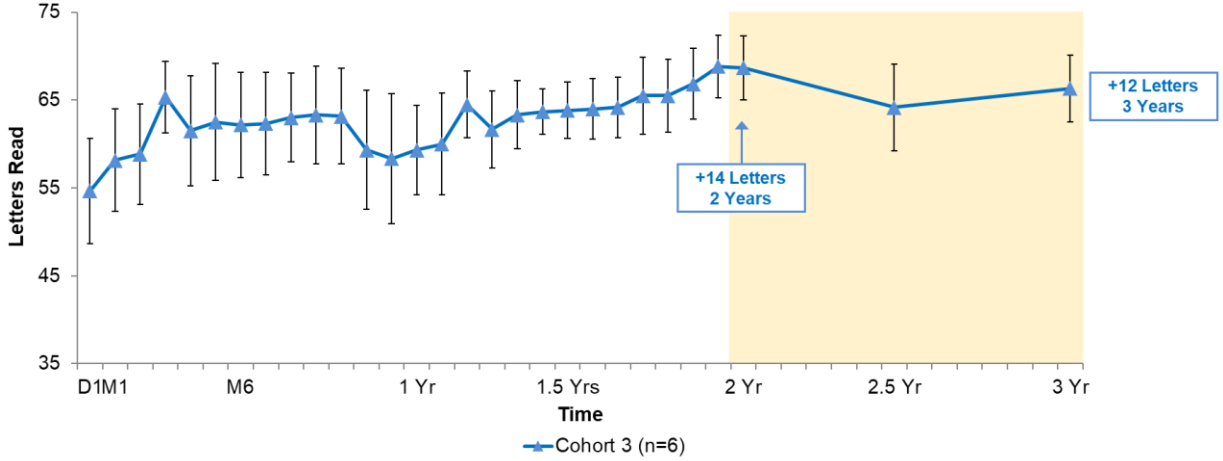
RGX-314 Phase I/IIa Trial: Stable to Improved VA, Including VA Improvement through 3 Years in Cohort 3

Best Corrected Visual Acuity (BCVA)



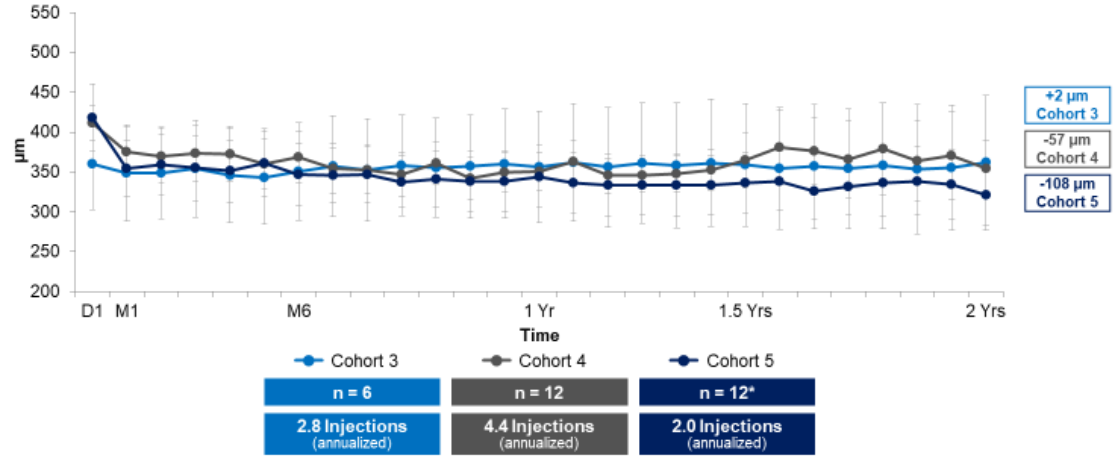
* One patient in Cohort 5 discontinued the study prior to the Week 22 visit and missing data post discontinuation was not imputed. Another patient in Cohort 5 has missed the visits due to COVID-19 from Week 50 through Week 74 and from Week 86 through Week 94. For this patient, missing visits were imputed using last observation carried forward (LOCF). Ten additional missing BCVA results were interpolated.

Best Corrected Visual Acuity (BCVA)



Stable to Improved Anatomy with Meaningful Reduction in anti-VEGF Injection Burden

Central Retinal Thickness (CRT) by Central Reading Center



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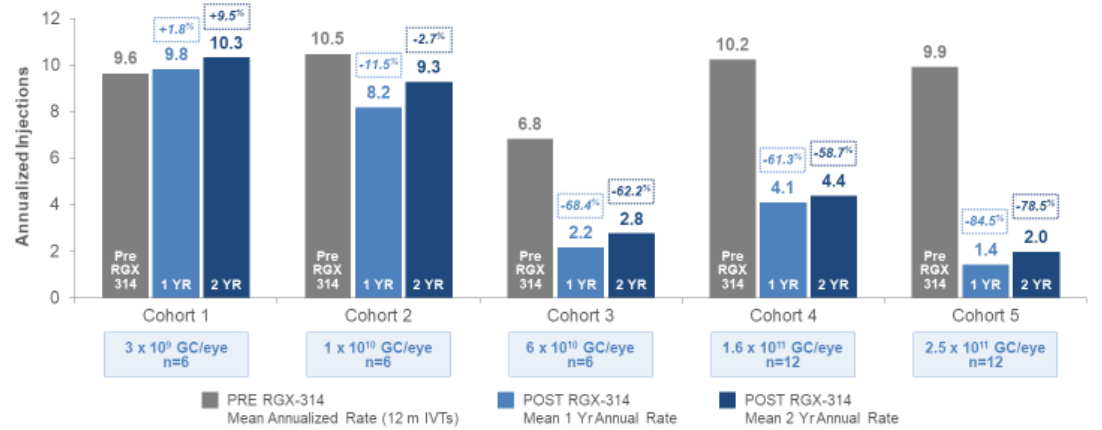
Annualized Injection Rate*



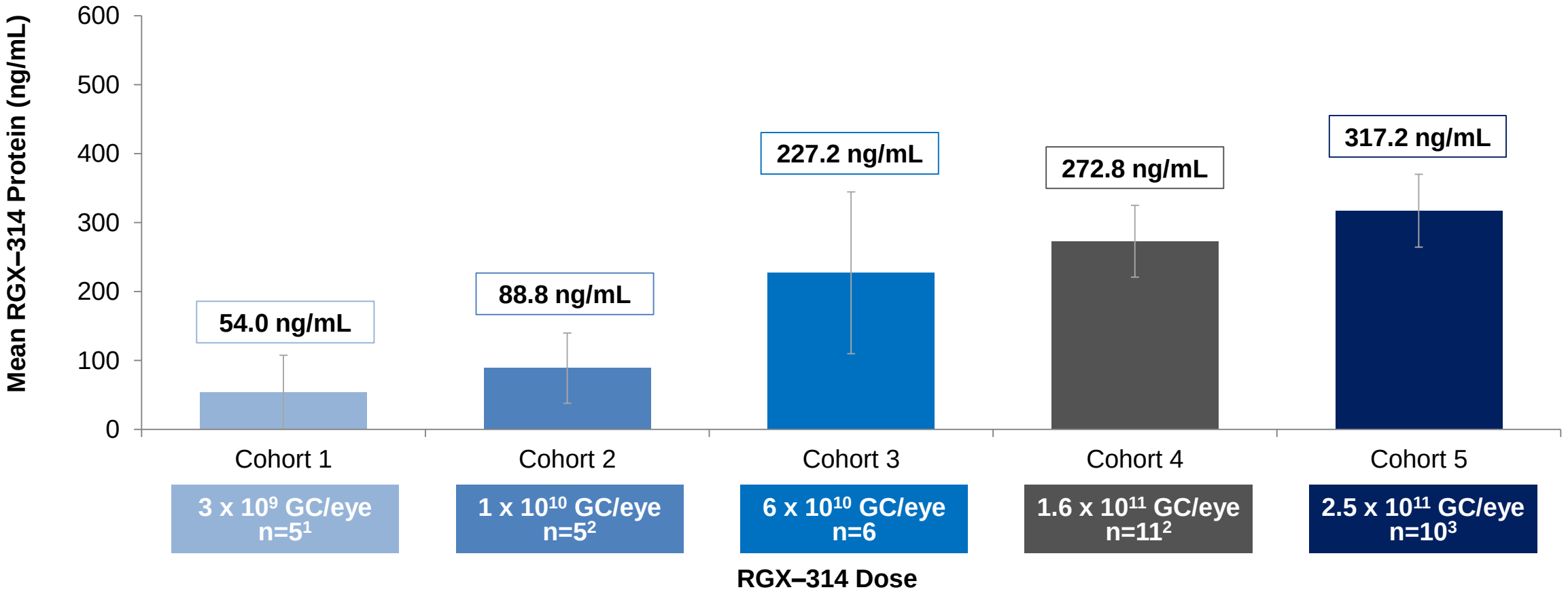
Retreatment Criteria: Any CNV-related increased, new, or persistent fluid; Vision loss of ≥5 letters associated with fluid; New ocular hemorrhage

* Prior annual rate is (Total # of prior IVTs)/(minimum(366 days, Duration between first ever IVT and Day 1)/365.25). Post RGX-314 annual rate is (Total # of IVTs on Study)/(Duration on Study/365.25) where on study is defined from RGX-314 administration to a specified cut-off date.

RGX-314 Protein Levels at Year 2 in All Cohorts

Dose-dependent intraocular RGX-314 protein levels across all 5 cohorts

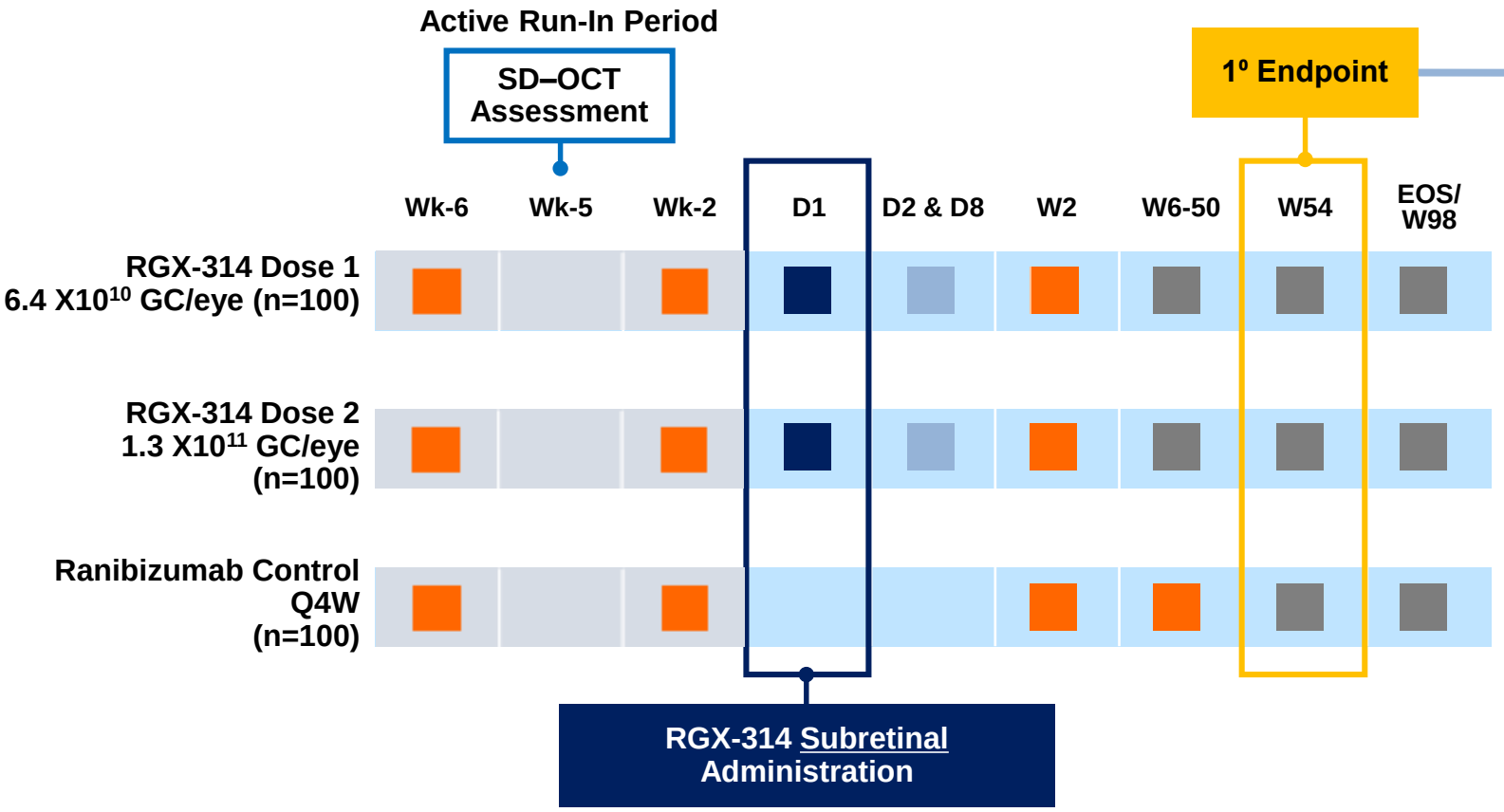
As Measured from Aqueous Samples by ECL

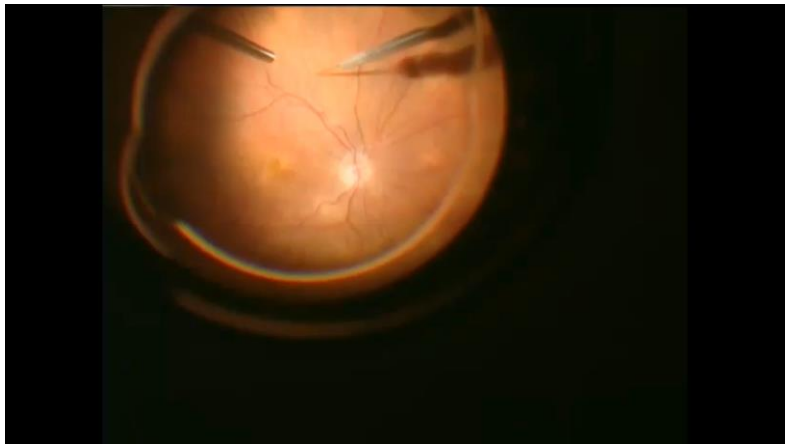


[1] One patient in Cohort 1 discontinued the study prior to the Week 22 visit.
[2] One patient did not have a year 2 sample taken.
[3] One patient in Cohort 5 discontinued the study prior to the Week 22 visit; another patient did not have a year 2 sample taken.

ATMOSPHERE™: RGX-314 Pivotal Trial in nAMD

Partially Masked, Controlled Pivotal Study





EOS: End of Study

Current Program Status for RGX–314

Subretinal

Phase I/IIa study for wet AMD is complete**;** Long-term follow-up continues

Pivotal trial for wet AMD is active and enrolling patients

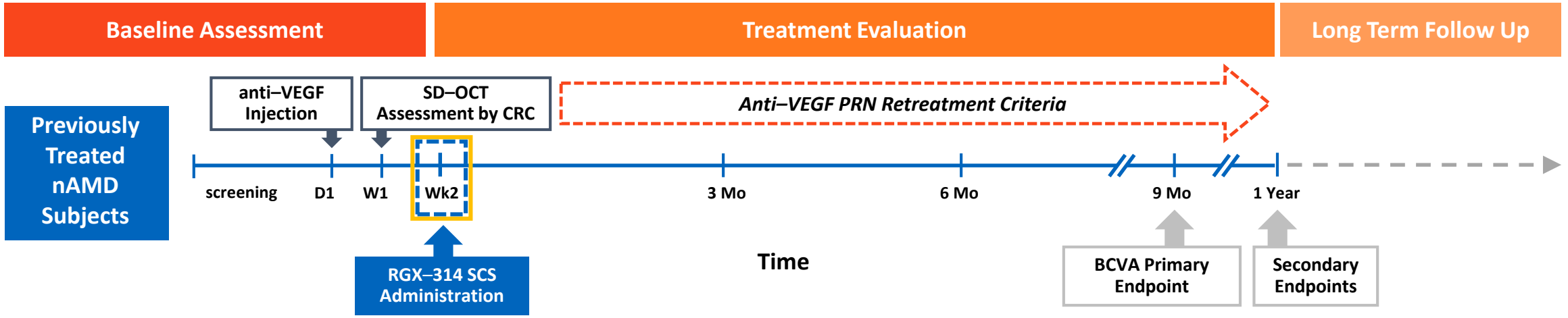
On-track to initiate **second pivotal trial** in Q4 2021

Suprachoroidal

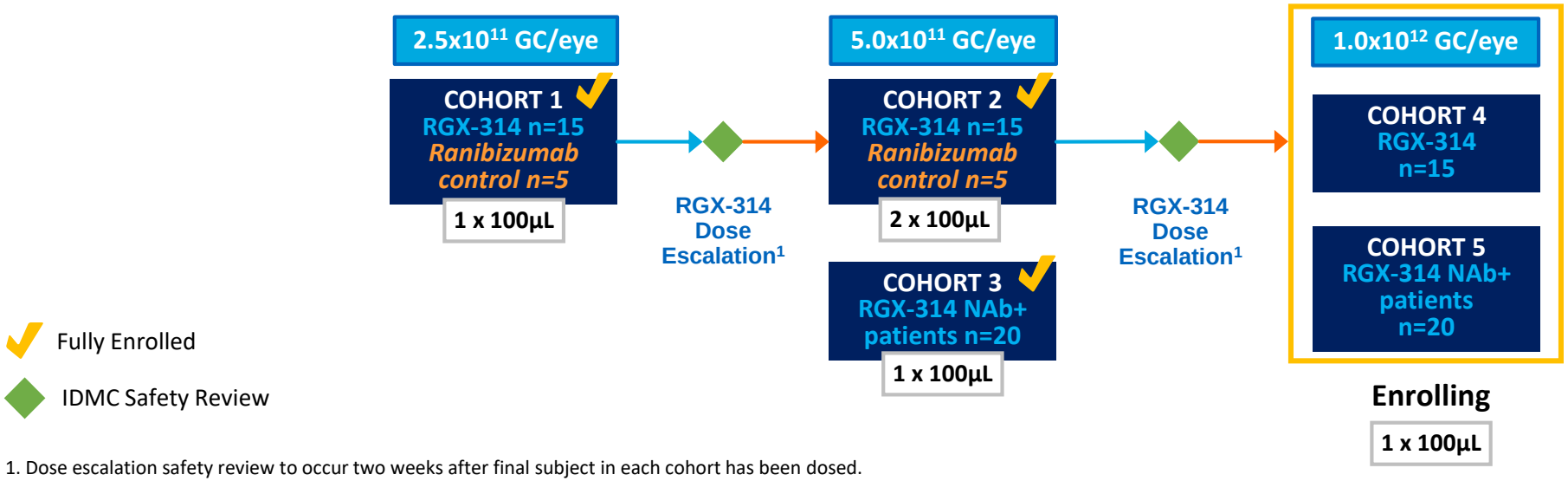
Phase II trial in wet AMD is ongoing

Phase II trial for diabetic retinopathy is ongoing

AAVIATE®: RGX-314 Phase II Clinical Trial in nAMD



No prophylactic steroids given throughout the study



1. 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

AAVIATE Baseline Characteristics (Cohort 1 – Cohort 3)

	Variable	Control Ranibizumab (N=10)	Cohort 1 (N=15)	Cohort 2 (N=15)	Cohort 3 (N=20)	Total (N=60)
BASELINE	**Mean Age** (Years)	**75.9**	**74.0**	**77.9**	**72.6**	**74.8**
	Screening BCVA (Letters)	**72.7**	**75.1**	**70.7**	**72.8**	**72.9**
	Screening OCT (Microns)	**240.3**	**269.2**	**275.7**	**265.8**	**264.9**
	Phakic n (%)	**3** (30.0%)	**6** (40.0%)	**7** (46.7%)	**10** (50.0%)	**26** (43.3%)
PRIOR THERAPY	**Months Since nAMD Diagnosis** (Mean)	**26.7**	**30.4**	**19.9**	**18.6**	**23.2**
	# Injections Since nAMD Diagnosis (Mean)	**13.4**	**20.6**	**11.1**	**9.7**	**13.4**
	# Injections in the Past Year (includes Day 1)	**6.8**	**7.2**	**6.0**	**6.2**	**6.5**
	Average Annualized Injections in the Past Year (includes Day 1)	**8.8**	**9.7**	**8.7**	**8.9**	**9.0**

Ocular variables refer to study eye only.
Average annualized injections in the past year is: (Total # of prior injections)/(minimum(366 days, Duration between first injection and Day 1)/365.25).

AAVIATE Safety Summary

- RGX–314 was well–tolerated in Cohorts 1–3 (n=50) with follow-up ranging from 2 – 12 months
  - 4 SAEs: None considered drug-related
  - No cases of chorioretinal vasculitis or occlusion, or hypotony were observed

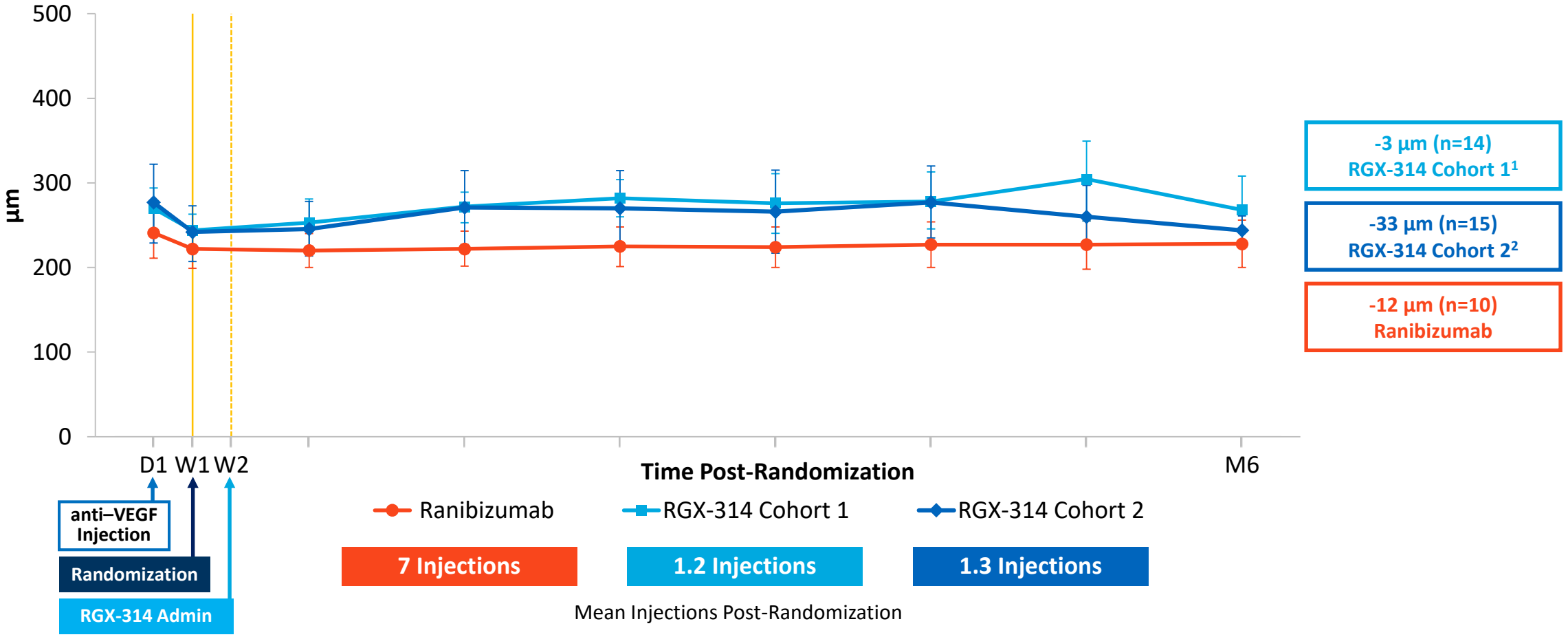
RGX-314 Common Ocular TEAEs[1] in the Study Eye through 6 Months:	Cohort 1 $2.5x10^{11}$ GC/eye 1 injection (N=15)	Cohort 2 $5.0x10^{11}$ GC/eye 2 injections (N=15)	Total (N=30)
Conjunctival hemorrhage	**5** (33.3%)	**3** (20.0%)	**8** (26.7%)
Intraocular Inflammation[2]	**4** (26.7%)	**3** (20.0%)	**7** (23.3%)
Worsening of nAMD[3]	**3** (20.0%)	**1** (6.7%)	**4** (13.3%)
Dry eye	**2** (13.3%)	**2** (13.3%)	**4** (13.3%)
Episcleritis[4]	**0** (0.0%)	**3** (20.0%)	**3** (10.0%)
Conjunctival hyperemia	**2** (13.3%)	**1** (6.7%)	**3** (10.0%)

Data cut: November 4, 2021

1. Includes AEs for total group ≥10% with onset up to 6m visit.
2. All mild, observed on slit lamp examination. Cohort 1: 3 patients presented with anterior cell (+0.5, +2, +2) and 1 patient presented with vitreous cell (trace). Cohort 2: 3 patients presented with anterior cell (+0.5, +1, +1). Resolved within days to weeks on topical corticosteroids.
3. All reported at one site.
4. All mild, presented 4 weeks post double injection and resolved within days to weeks on topical corticosteroid or NSAID treatment.

Cohorts 1 and 2: Mean CRT from Day 1 (Screening) Through Month 6

Central Retinal Thickness (CRT) 95%CI

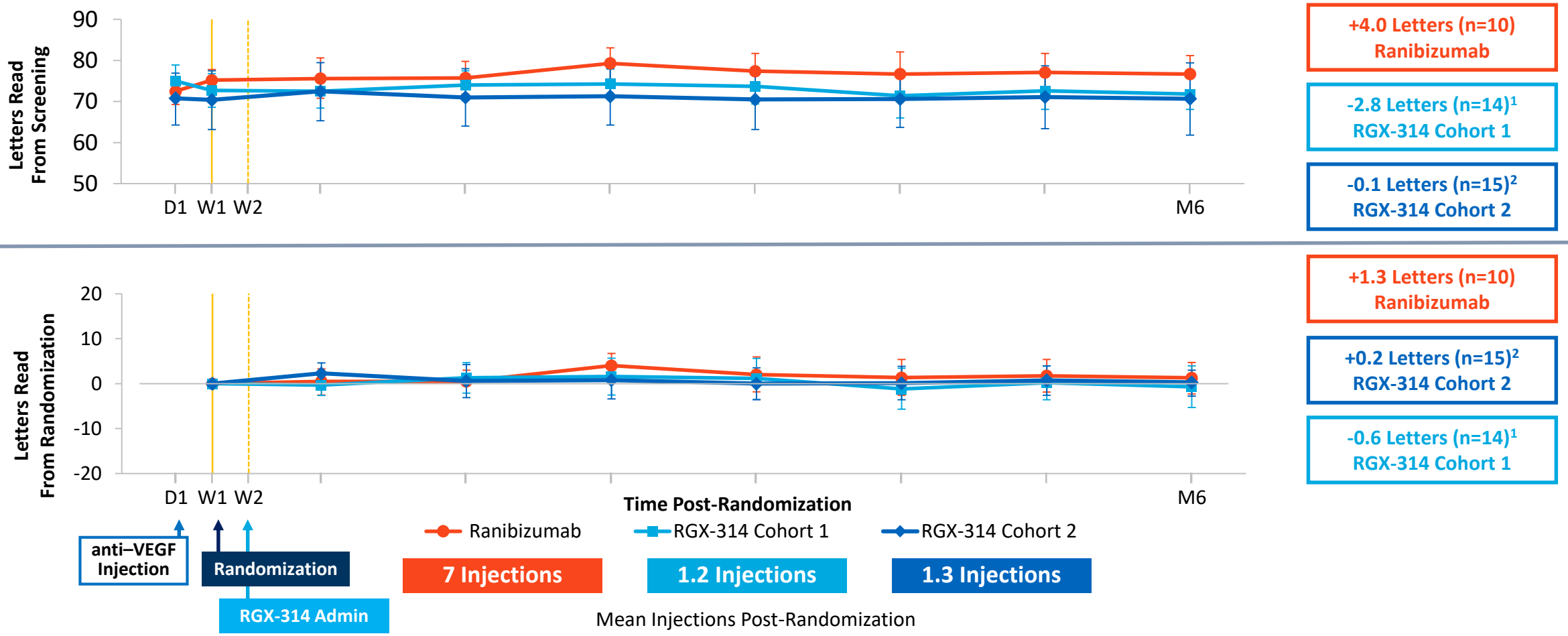


Data cut: November 4, 2021

1. One patient discontinued the study after Week 12, and only data up to week 12 is included for the subject. For one patient who has missing Weeks 8 and 28 visits, the missing data has been interpolated using the average of before and after the missing visit.
2. For one patient who missed the Week 28 visit, the missing data has been interpolated using the average of before and after the missing visit.

Cohort 1 and 2: Mean Change in BCVA Through Month 6

Best Corrected Visual Acuity (BCVA) 95% CI



Data cut: November 4, 2021

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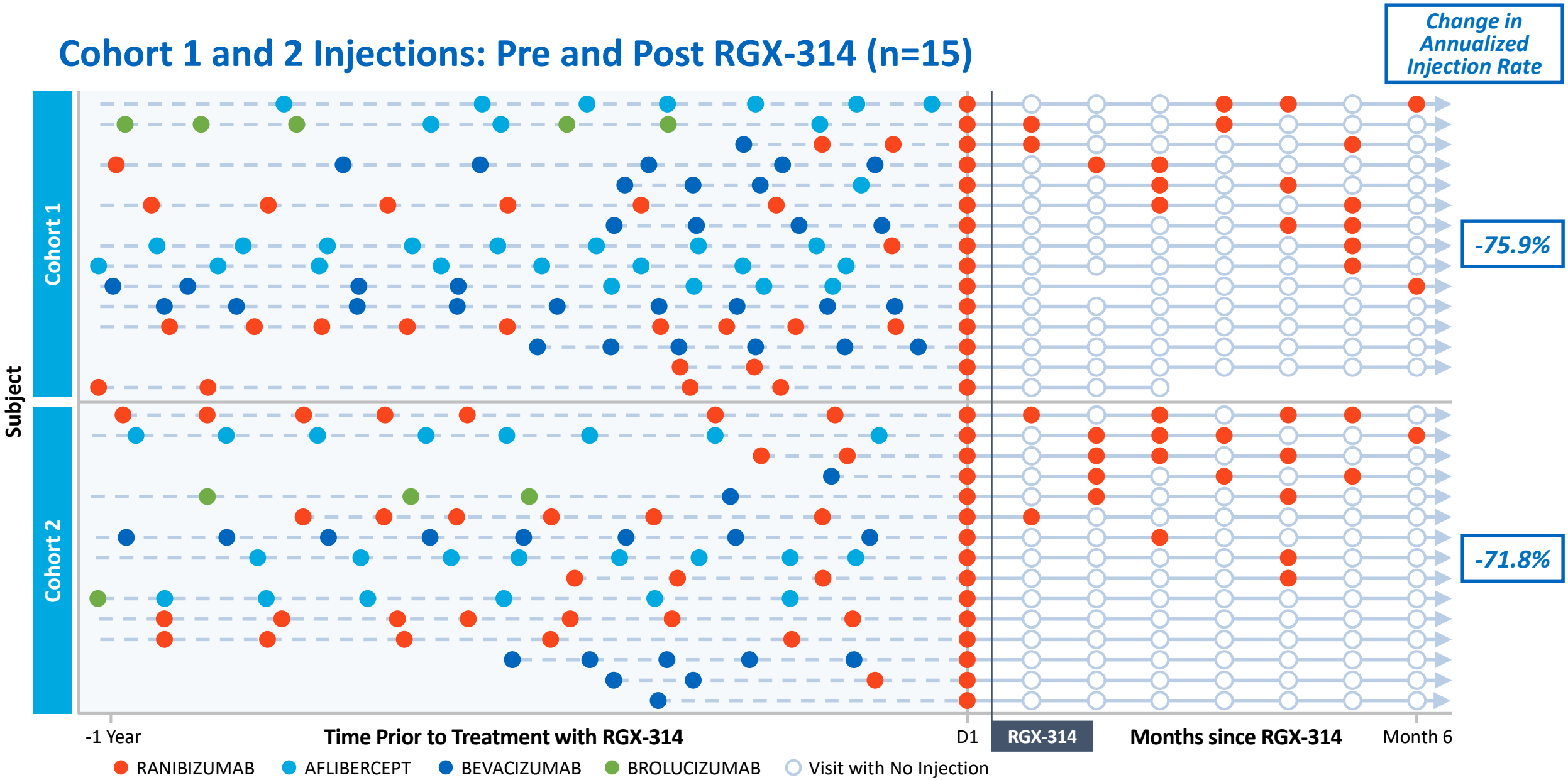
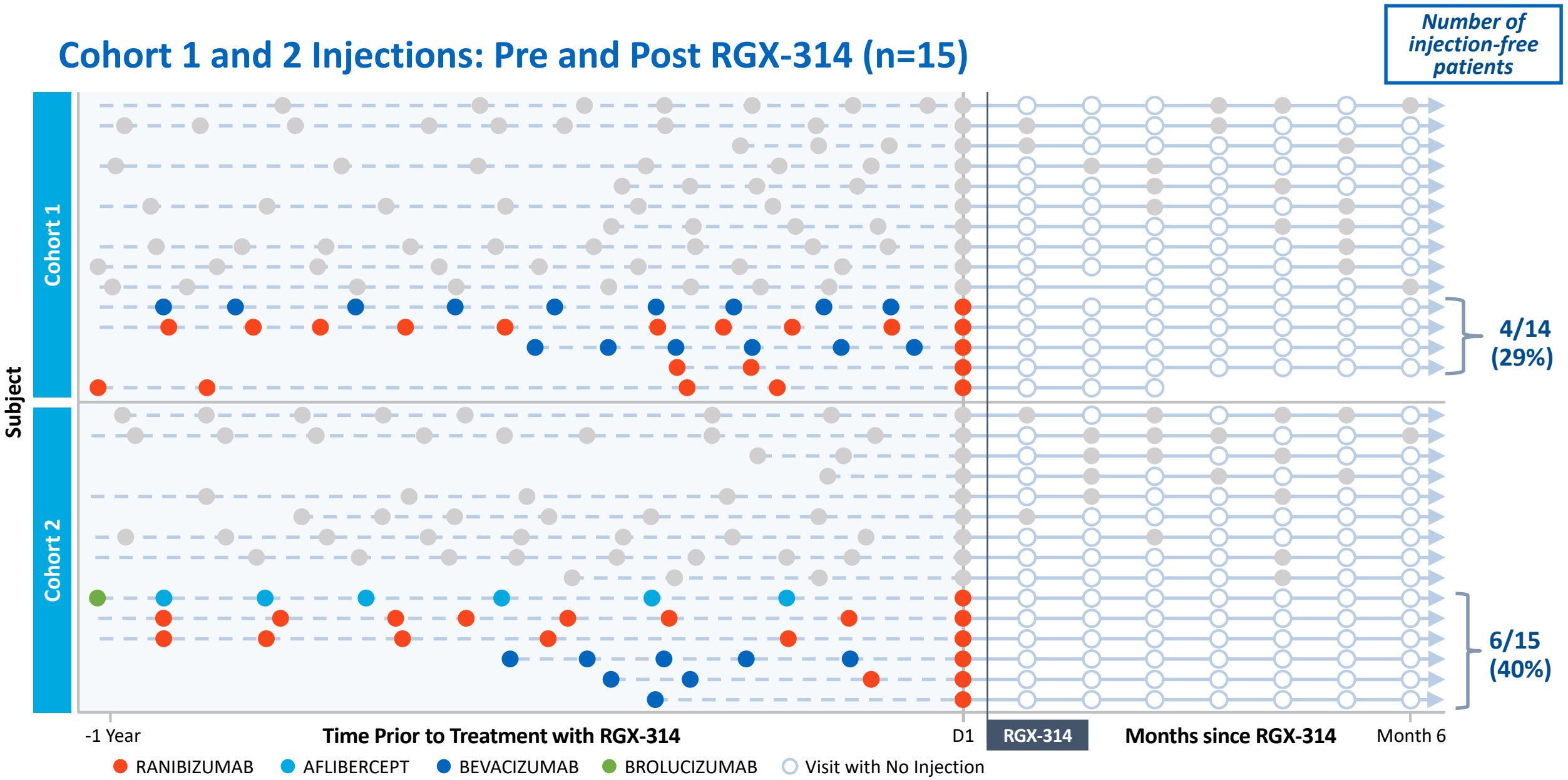
2. For one patient who has missing Weeks 8 and 28 visits, the missing data has been interpolated using the average of before and after the missing visit.

Cohort 1 and 2 Injections: Pre and Post RGX-314 (n=15)



Change in annualized injection rate is the difference between historical annualized injection rate and on-study annualized injection rate up to 6 months post-RGX-314.
Historical annualized injection rate is (Total # of prior injections)/(minimum(366 days, Duration between first injection and Day 1)/365.25).
On-study annualized injection rate is (Total # of injections on Study)/(Duration on Study/365.25) where on-study is defined from post-D1 to a specified cut-off date.

Cohort 1 and 2 Injections: Pre and Post RGX-314 (n=15)



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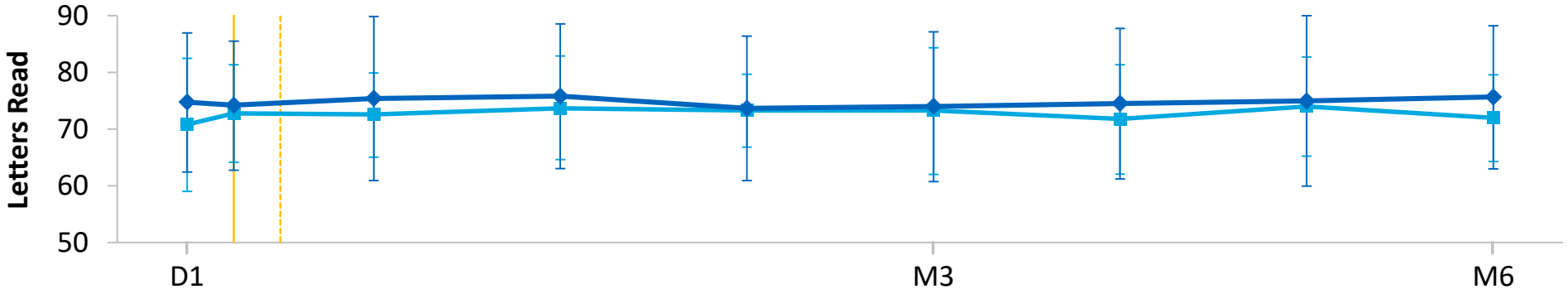
Historical annualized injection rate is (Total # of prior injections)/(minimum(366 days, Duration between first injection and Day 1)/365.25).
On-study annualized injection rate is (Total # of injections on Study)/(Duration on Study/365.25) where on-study is defined from post-D1 to a specified cut-off date.

Cohorts 1 and 2 Subjects with No Anti-VEGF Injections over 6 Months

Mean BCVA and CRT from Day 1

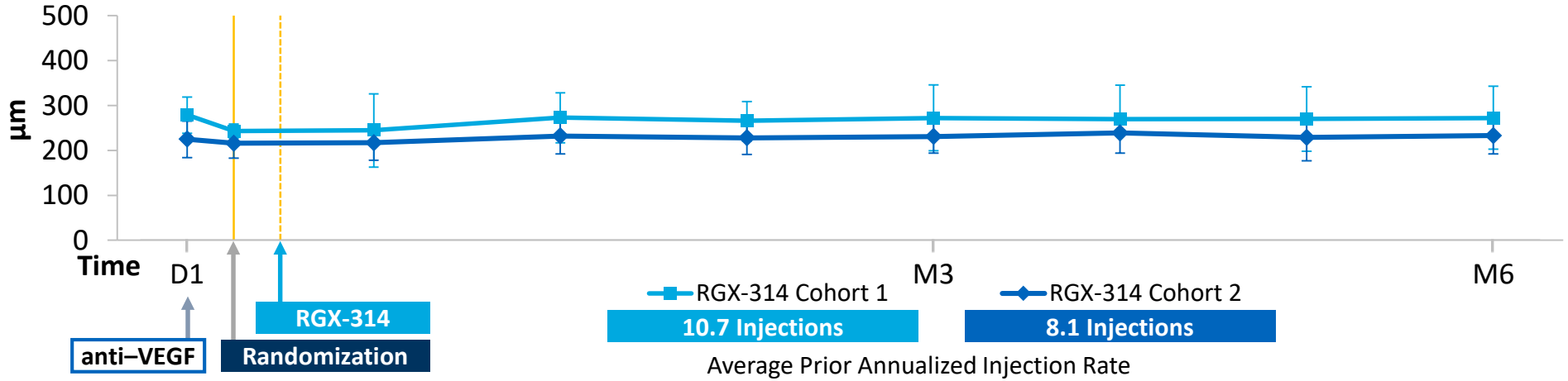
Best Corrected Visual Acuity (BCVA) 95% CI



+1.0 Letters (n=6)
RGX-314 Cohort 2[1]

+1.3 Letters (n=4)
RGX-314 Cohort 1

Central Retinal Thickness (CRT) 95% CI



-6.0 µm (n=4)
RGX-314 Cohort 1

+8.0 µm (n=6)
RGX-314 Cohort 2[1]

Data cut: November 4, 2021

1. For one patient who missed their Week 28 visit, the missing data has been interpolated using the average of before and after the missing visit.

Summary of Results from the Phase II AAVIATE® nAMD Study

RGX-314 Cohorts 1-3 (n=50): Safety

- Suprachoroidal RGX-314 has been well-tolerated

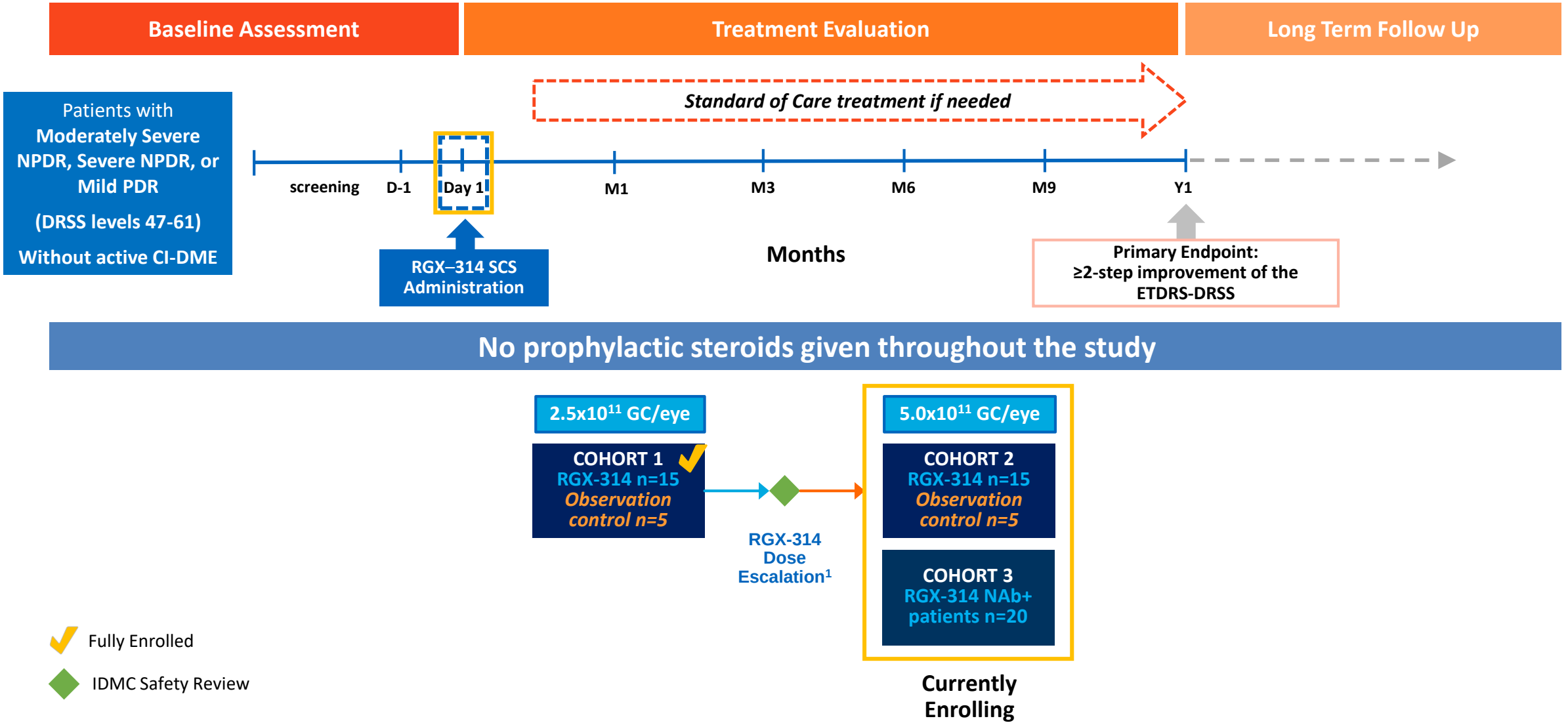
RGX-314 Cohorts 1-2 (n=30): 6 Month Results

- Similar incidence of intraocular inflammation observed among cohorts with dose escalation
  - All mild and resolved within days to weeks with topical corticosteroids

- RGX-314 treated patients had stable vision and retinal thickness with a meaningful reduction (>70%) in treatment burden
  - 29% in Cohort 1 were injection-free
  - 40% in Cohort 2 were injection-free

AAVIATE is currently enrolling Cohorts 4 and 5
(Dose level 3: $1x10^{12}$ GC/eye, NAb- and NAb+ patients)

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



1. 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. 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%)
PRIOR THERAPY	**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)
  - 1 SAE: not considered drug-related:
    - Vitreous hemorrhage in an untreated *fellow eye*
- **Common ocular TEAEs[1] in the study eye were not considered drug-related and were predominantly mild**:
  - Conjunctival hyperemia (2/15, 13%)
  - Conjunctival hemorrhage (2/15, 13%)
- One case of mild episcleritis[2] that resolved with topical corticosteroids
- **No intraocular inflammation** observed on slit-lamp examination
- **Stable BCVA**

	Observational Control (N=5)	Cohort 1 $2.5x10^{11}$ GC/eye (N=15)
Mean change in BCVA at M3	**-0.4 letters**	**+2.6 letters**

Data cut: September 29, 2021

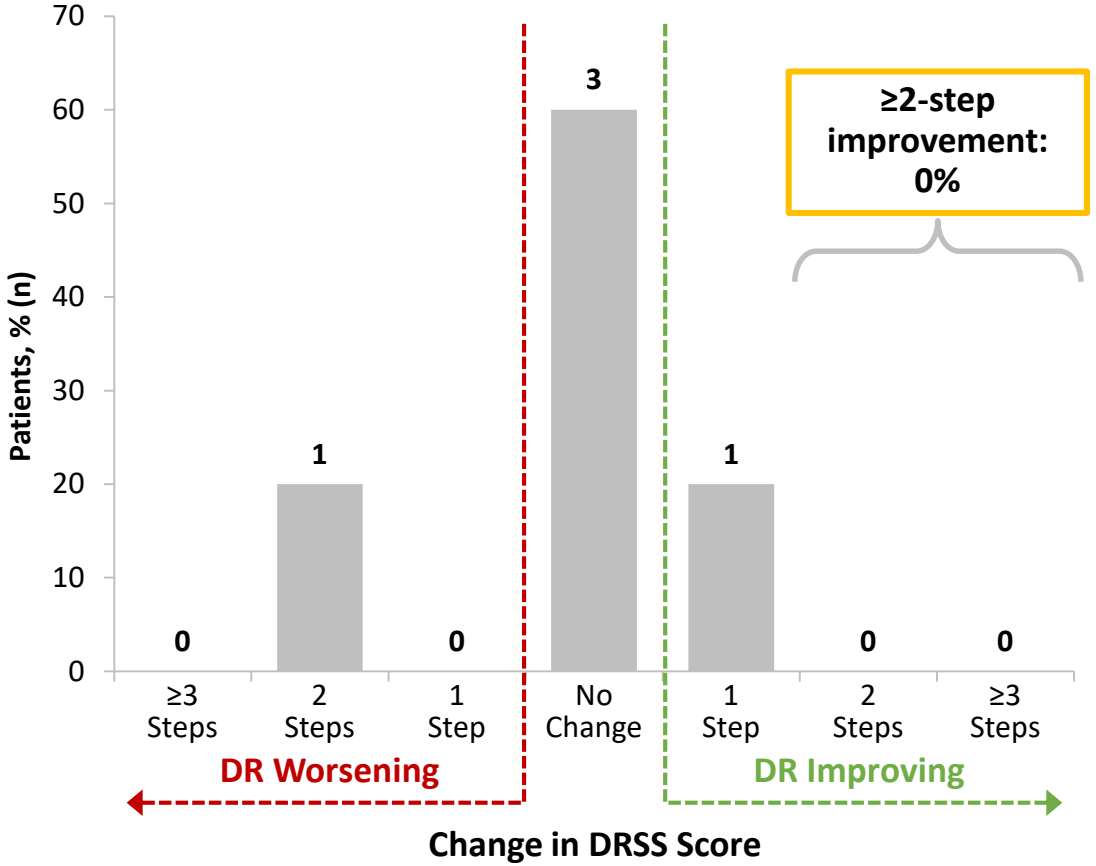
1. Common ocular TEAEs defined as ≥ 10% of RGX-314 treated study eyes.
2. Onset was 2-weeks post-dosing.

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

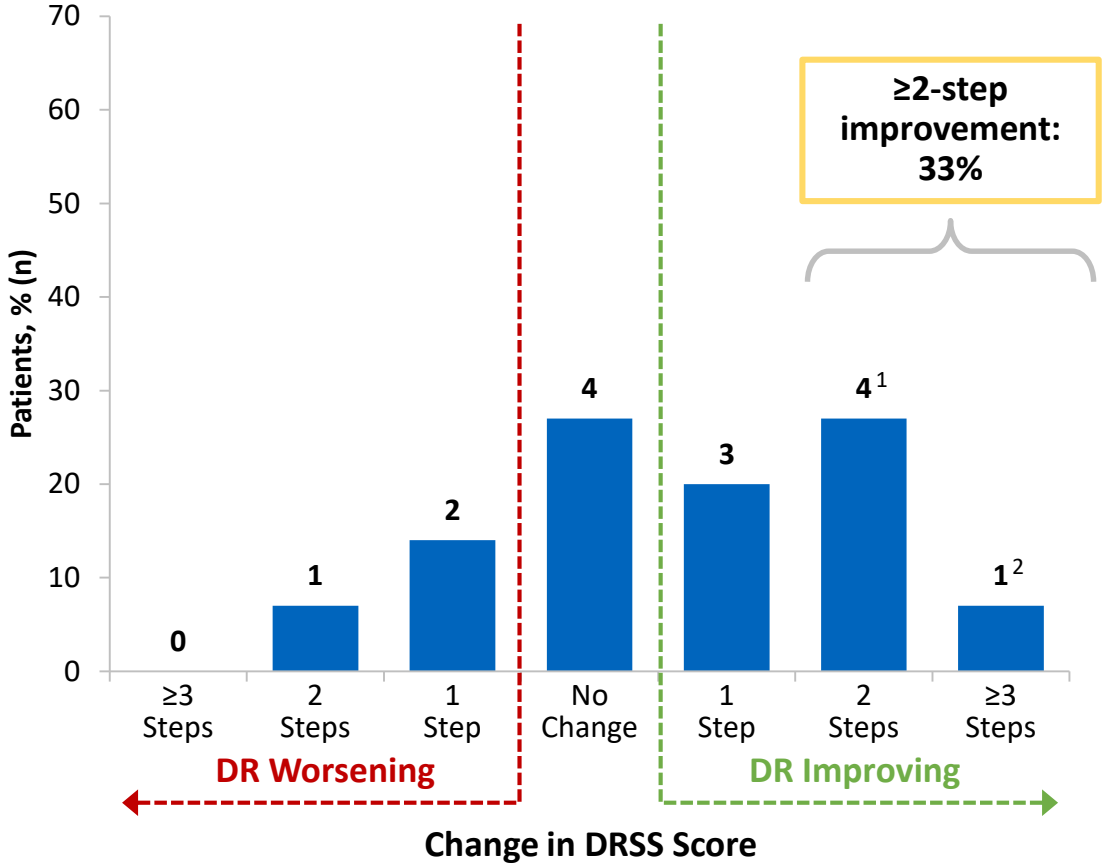
Cohort 1: Change in DRSS at Month 3

33% of RGX-314 Treated Patients Achieved a ≥2-Step Improvement

Observational Control (n=5)



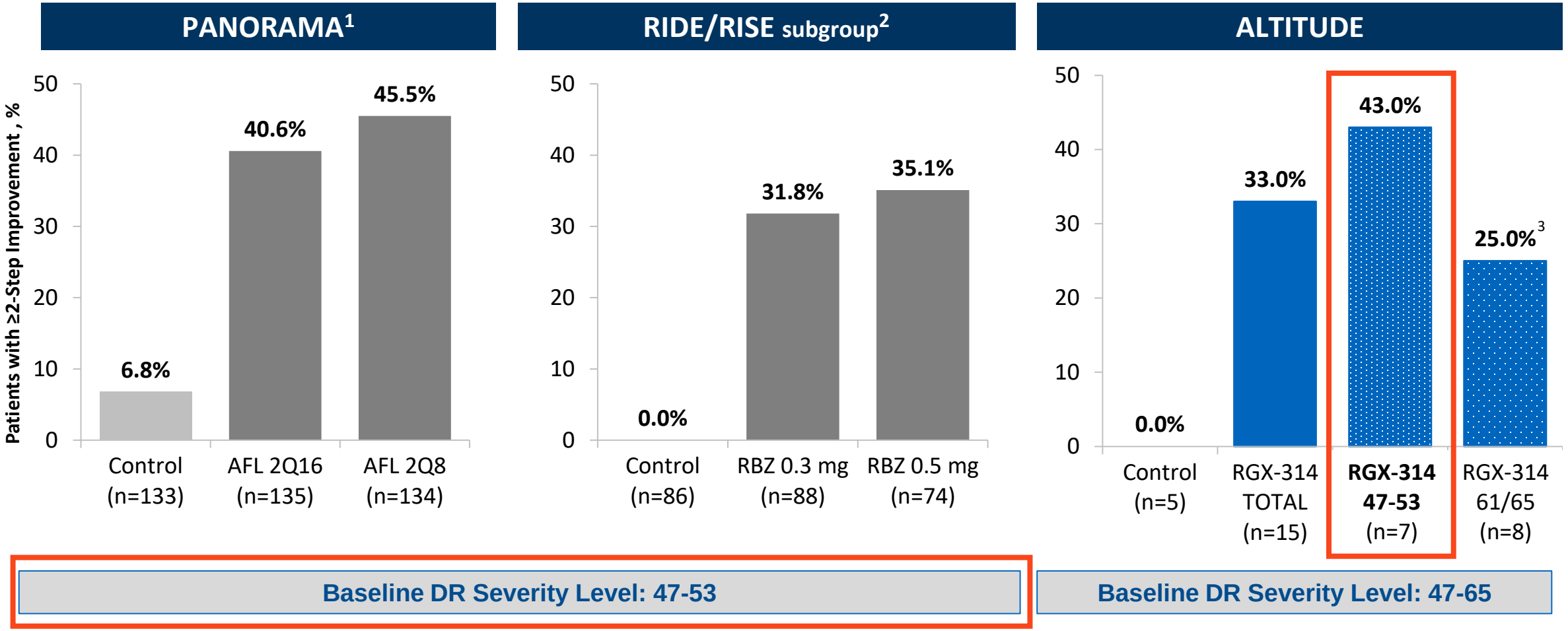
RGX-314 (n=15)



Data cut: September 29, 2021

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.

How do ALTITUDE Cohort 1 DRSS Outcomes at 3 Months Compare to Prior Clinical Trials?

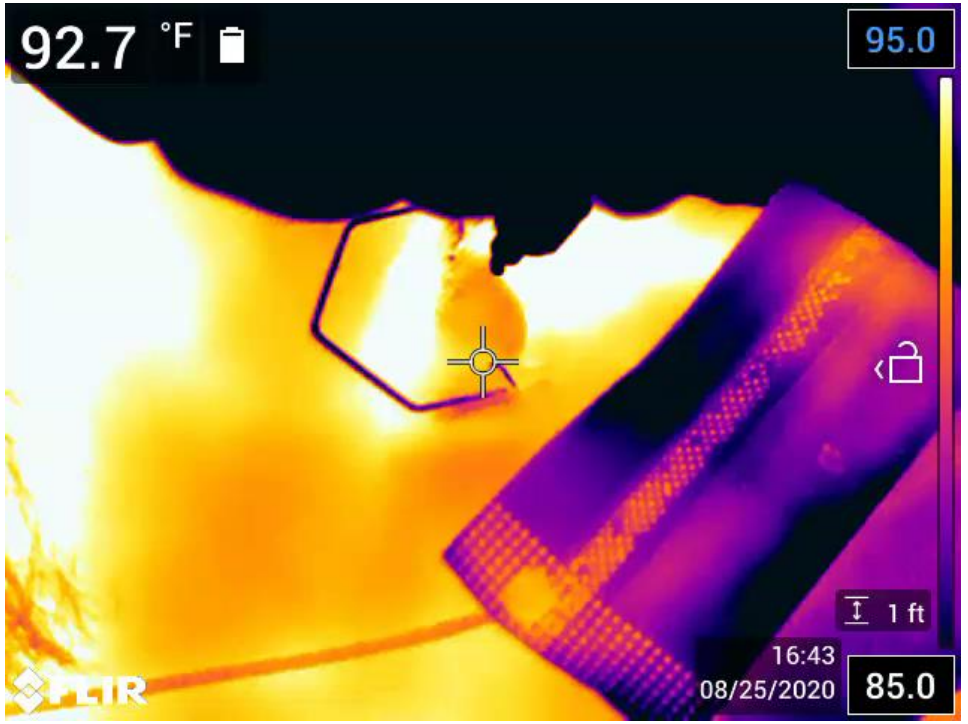


Data cut: September 29, 2021

1. DRSS assessment at the 12 week timepoint was after 3 Q4W aflibercept (AFL) injections; EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. March 2021.
2. DRSS assessment at the 3 month timepoint was after 3 Q4W ranibizumab (RBZ) injections; Wykoff CC et al. Ophthalmology Retina. 2018 DOI: (10.1016/j.oret.2018.06.005).
3. One patient had a 4-step improvement. Another 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.

Summary of Initial Results from the Phase II ALTITUDE™ DR Study

- Suprachoroidal RGX-314 has been **well-tolerated** in Cohort 1 ($2.5x10^{11}$ GC/eye; n=15)
- **No intraocular inflammation**
  - No prophylactic corticosteroids administered
- In RGX-314 treated eyes, **33% achieved a ≥2 step improvement** in DRSS at 3 months



Video: M. Barakat

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

Data cut: September 29, 2021

Current Program Status for RGX–314

Subretinal

Phase I/IIa study for wet AMD is complete**;** Long-term Follow-up continues

Pivotal trial for wet AMD is active and enrolling patients

ATMOSPHERE

On-track to initiate **second pivotal trial** in Q4 2021

Suprachoroidal

Phase II trial in wet AMD is ongoing

AAVIATE

Phase II trial for diabetic retinopathy is ongoing

ALTITUDE