Subretinal Delivery of RGX-314 for Neovascular AMD: End of Phase I/IIa Study Results

Allen Ho, MD, FACS
Retina Society, 2021

Co-authors: Robert Avery, MD; David Brown, MD; Peter Campochiaro, MD; Jorge Calzada, MD; Jeff Heier, MD; Stephen Huddleston, MD; Arshad Khanani, MD, MA; Albert Maguire, MD; Dante Pieramici, MD, Charles C. Wykoff, MD, PhD

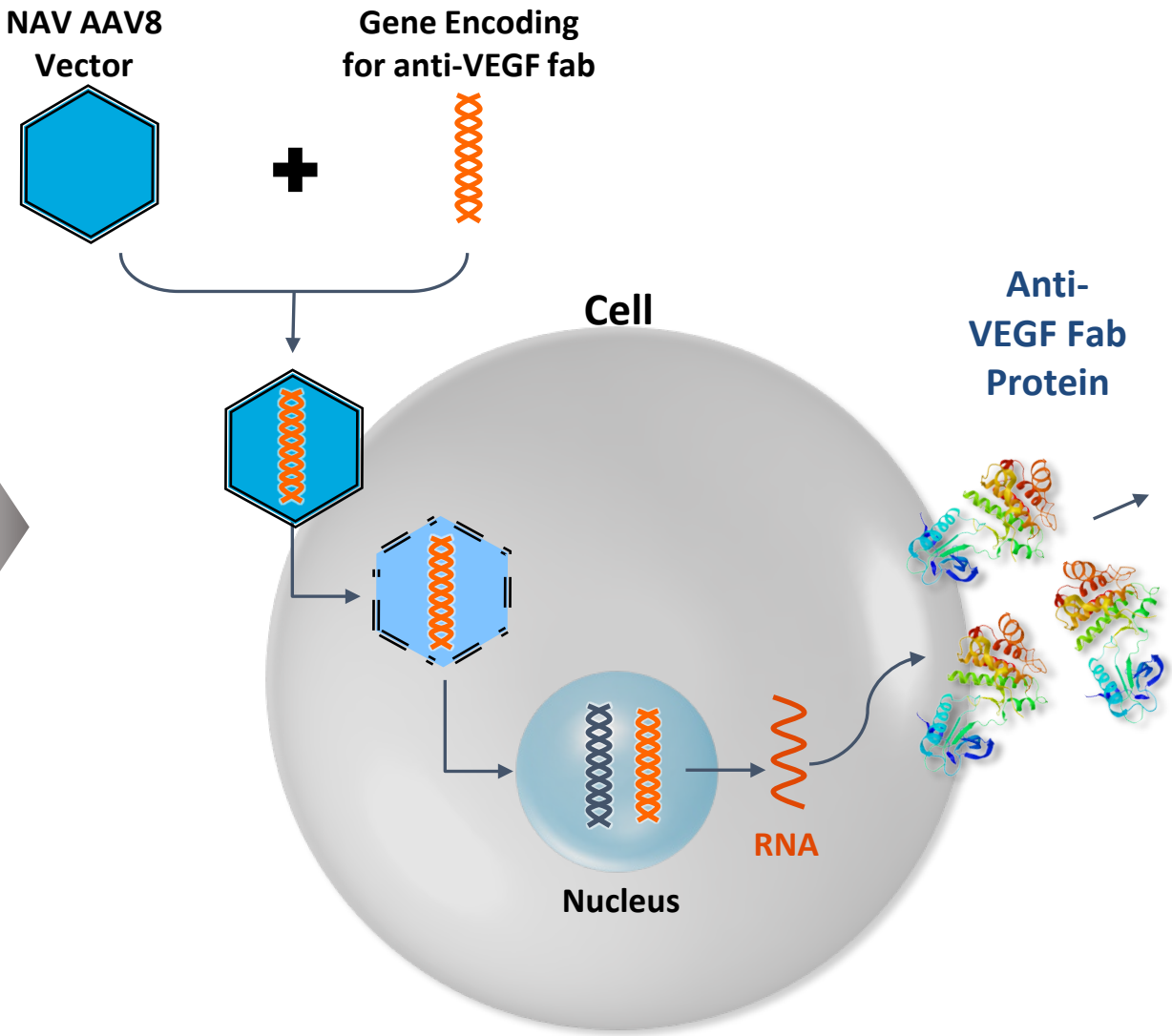
Disclosures

Adverum: C, G
Aerie: C, G
AGTC: C, G
Alcon Laboratories, Inc: C, G
Aldeyra: C, G
Allergan: C, G
Apellis: C, G
Asclepix: C, G
Atsena: C, G
Beaver-Visitec International, Inc.: C
Chengdu Kanghong Biotechnology: C, G
Clearside: C
Covalent Medical, LLC: O
Dompe C
Eyevensys C
Genentech: C, G
Graybug: C, G
Gyroscope: C, G, P
Iveric: C, G
Janssen / Johnson & Johnson: C, G
Lineage: C, G
Lumithera: G
MeiraGtx: G, C
National Eye Institute: G
Notal: C, G
Novartis: G
Ocular Therapeutics: C
ONL: C, O
ProQR: G
Regeneron Pharmaceuticals, Inc.: C, G
REGENXBIO: C, G

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

RGX-314 Uses a Novel AAV8 Vector to Deliver an anti-VEGF Fab

RGX-314 is Designed to Deliver a Gene Encoding for an Anti-VEGF Fab Protein



AAV: Adeno-associated Virus

RGX-314 Phase I/IIa Clinical Trial in nAMD

Objectives

Primary

- To determine the safety and tolerability of RGX-314 in previously treated patients with nAMD through 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”)

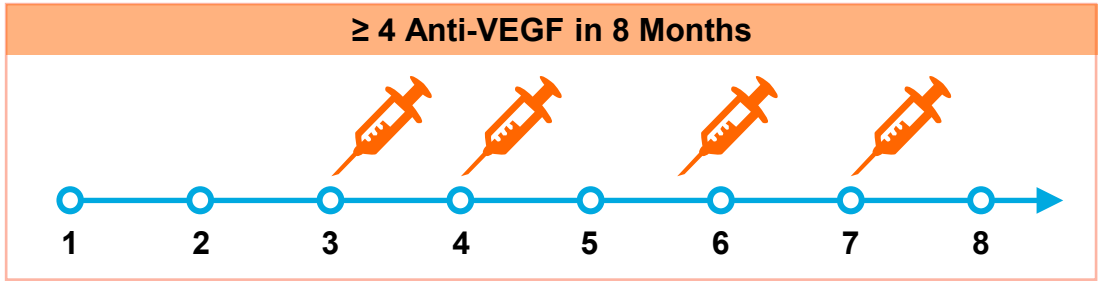
Rescue: New or Persistent Fluid/ Loss in Vision

- Per the Investigator's discretion

Subjects: 42 Patients dosed subretinally

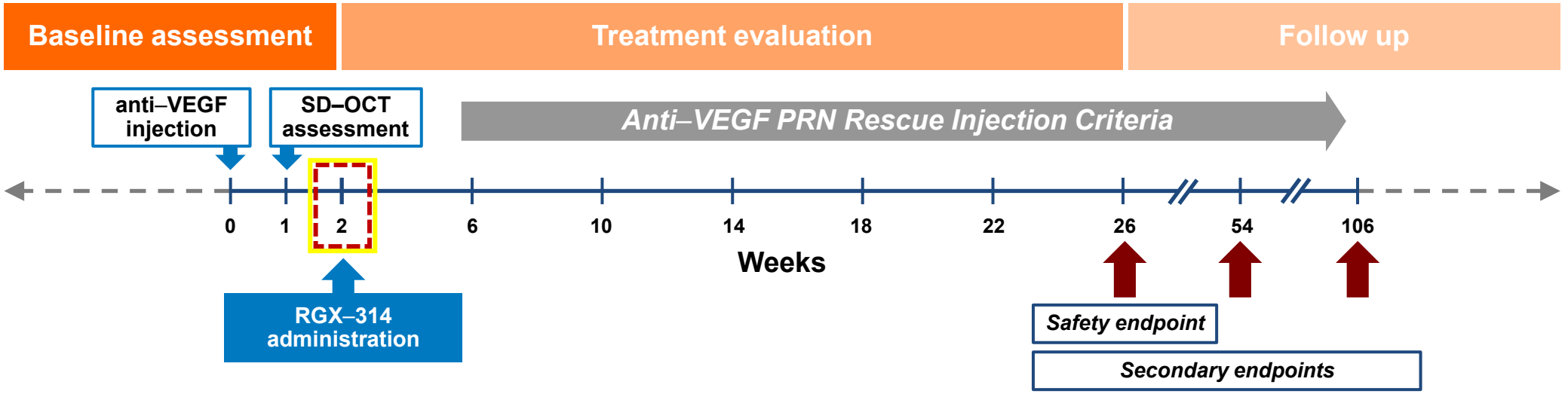
- **8 study sites** across the United States

Key Inclusion Criteria



- Male or female ≥ 50 to 89 years of age
- Documented **nAMD with response to anti-VEGF (ranibizumab) 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

RGX-314 Phase I/IIa nAMD Study Has Fully Enrolled 5 Dose Cohorts



Previously treated patients 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 = 12 ✓	Safety review[1]	Dose 5 n = 12 ✓
$3x10^9$ GC/eye		$1x10^{10}$ GC/eye		$6x10^{10}$ GC/eye		$1.6x10^{11}$ GC/eye		$2.5x10^{11}$ GC/eye

[1] Dose escalation safety review to occur four weeks after final patient in each cohort has been dosed
SD-OCT = spectral domain optical coherence tomography

RGX-314 Phase I/IIa Clinical Trial in nAMD
Anti-VEGF Retreatment Allowed for Any Fluid or Disease Activity

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:

Any CNV-related **increased, new, or persistent fluid**

Vision loss of ≥5 letters associated w/ fluid

New ocular **hemorrhage**

Subjects Enrolled in the Phase I/IIa Trial Were Chronically Treated

	Variable	Cohort 1 (n=6)	Cohort 2 (n=6)	Cohort 3 (n=6)	Cohort 4 (n=12)	Cohort 5 (n=12)	Total (n=42)
BASELINE	**Mean Age (Years)**	**78.2**	**78.0**	**80.0**	**80.3**	**81.6**	**80.0**
	Baseline BCVA (Snellen equivalents)	53.7 (20/100)	50.7 (20/100)	54.7 (20/80)	61.3 (20/63)	54.3 (20/80)	55.7 (20/80)
	Baseline OCT (reading center)	**361.7** (n=6)	**413.2** (n=6)	**359.8** (n=6)	**411.3** (n=12)	**418.3** (n=12)	**399.1** (n=42)
	Baseline serum AAV8 Nab+ with titer >1:10	**2** (33.3%)	**3** (50.0%)	**4** (66.7%)	**4** (33.3%)	**5** (41.7%)	**18** (42.9%)
PRIOR THERAPY	**Months Since First anti-VEGF Injection**	**53.5**	**59.3**	**71.6**	**58.1**	**45.8**	**56.0**
	# Injections Since Diagnosis (Mean)	**40.7**	**32.5**	**34.2**	**35.7**	**26.7**	**33.1**
	Average Annualized Injections Prior to Entry	**9.6**	**10.5**	**6.8**	**10.2**	**9.9**	**9.6**

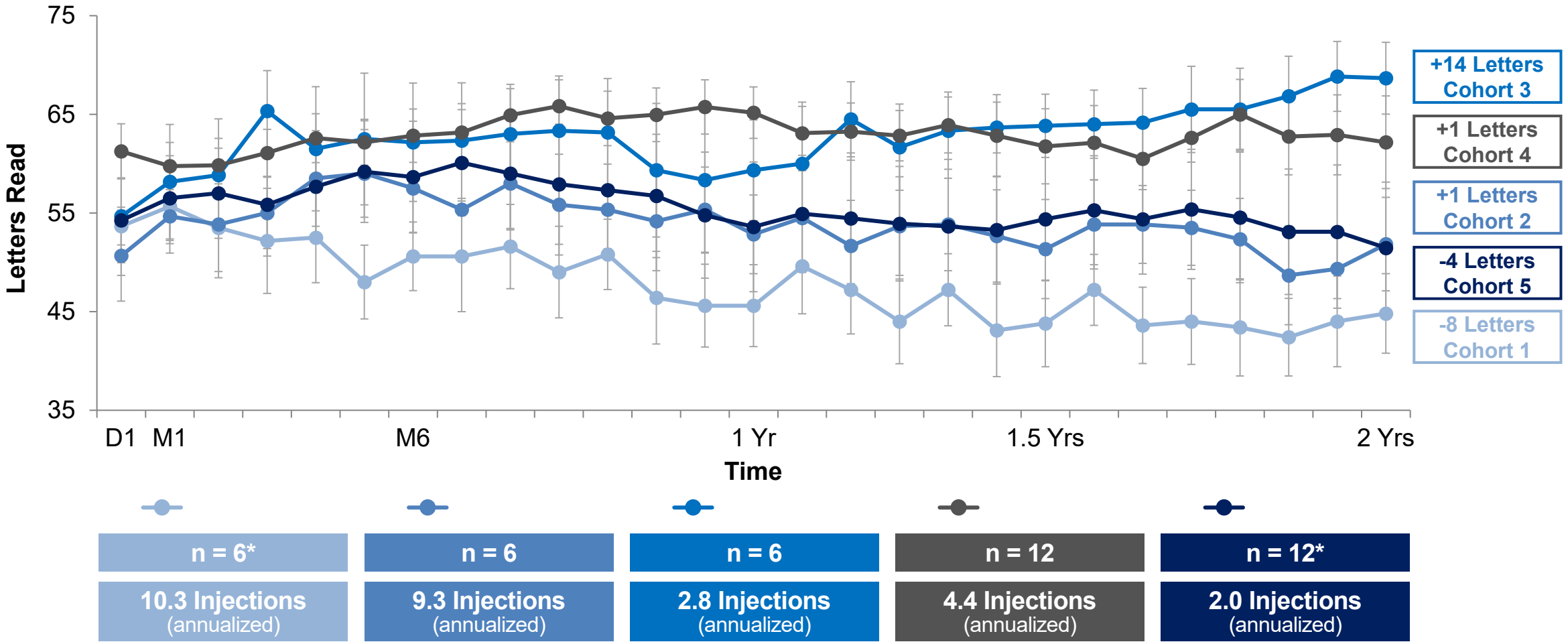
RGX-314 Phase I/IIa nAMD: Overall Safety

- **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 13th, 2021: Preliminary analysis - data subject to further verification at database lock
[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

Mean BCVA Over 2 Years in All 5 Cohorts

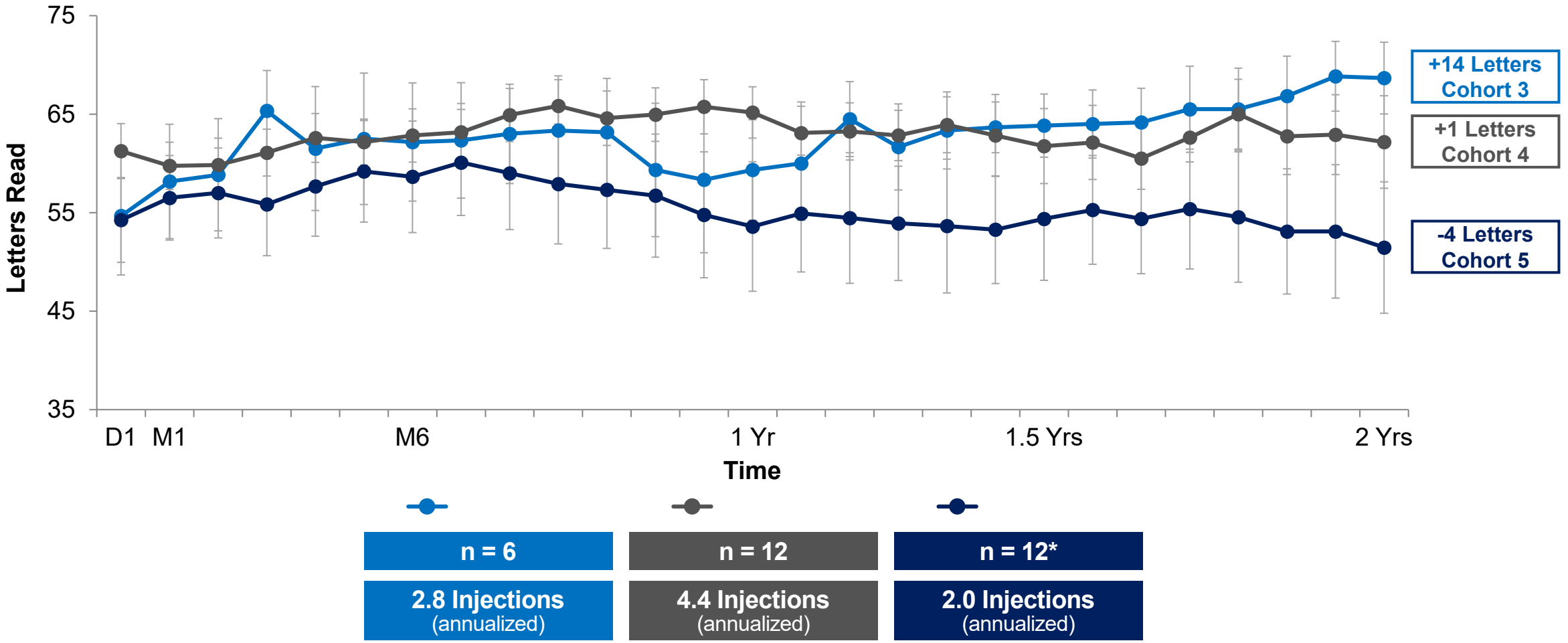
Best Corrected Visual Acuity (BCVA)



* One patient in Cohort 1 and one patient in Cohort 5 discontinued the study, both prior to visits at Week 22, and missing data post discontinuation was not used in the analysis. 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). Twelve additional missing BCVA results were interpolated.

Mean BCVA Over 2 Years in Cohorts 3-5

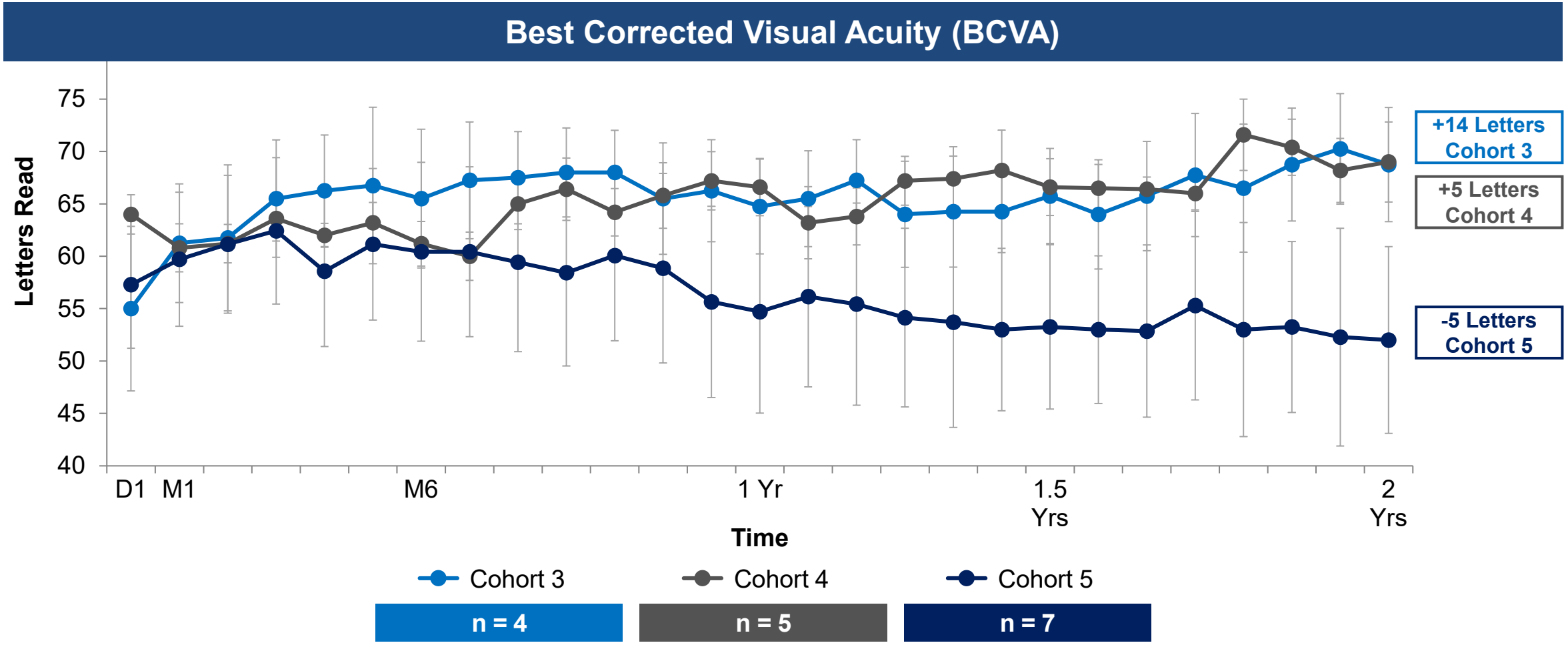
Best Corrected Visual Acuity (BCVA)



* 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.

Cohort 3-5: Mean BCVA Over 2 Years (C3-5)

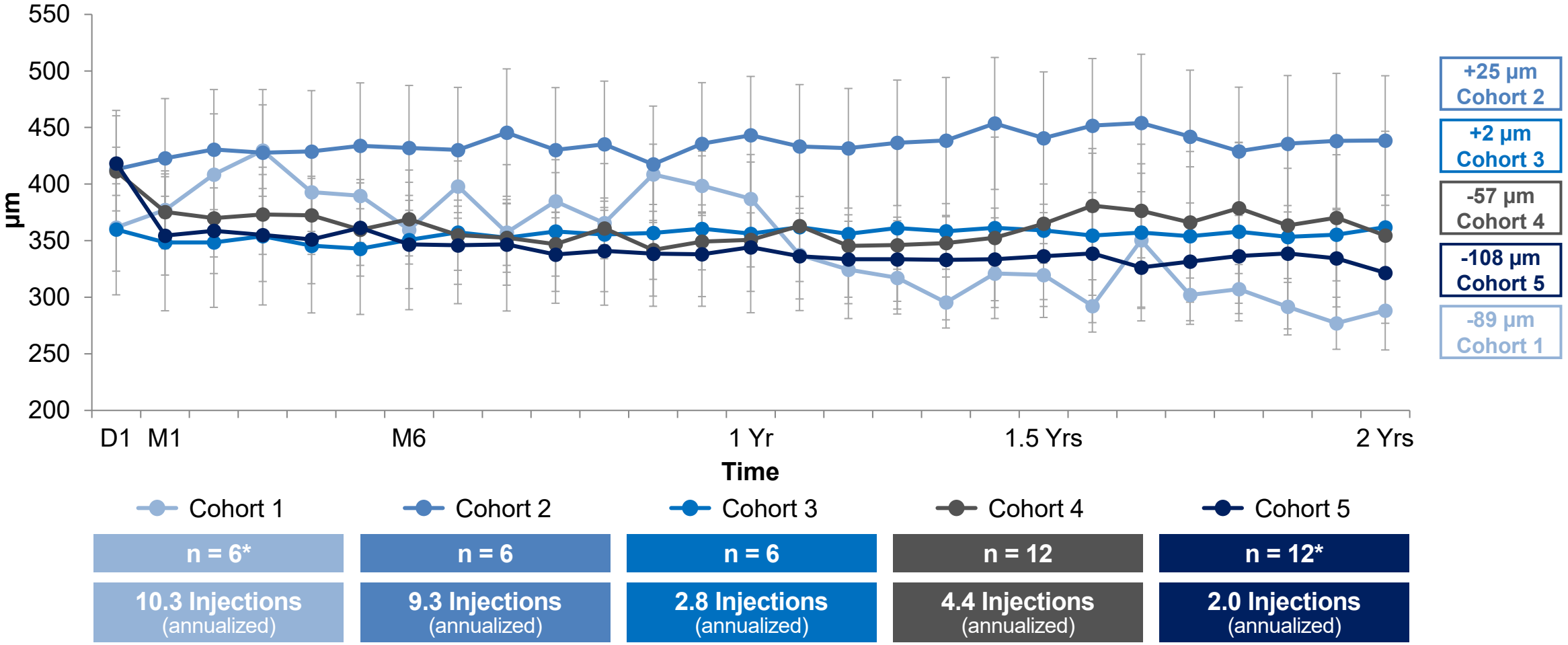
Subjects with no anti-VEGF injections within Last 12 months of the Study



Note: A patient in Cohort 5 has missed 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). Four additional missing BCVA results were interpolated.

Mean CRT Over 2 Years in All 5 Cohorts

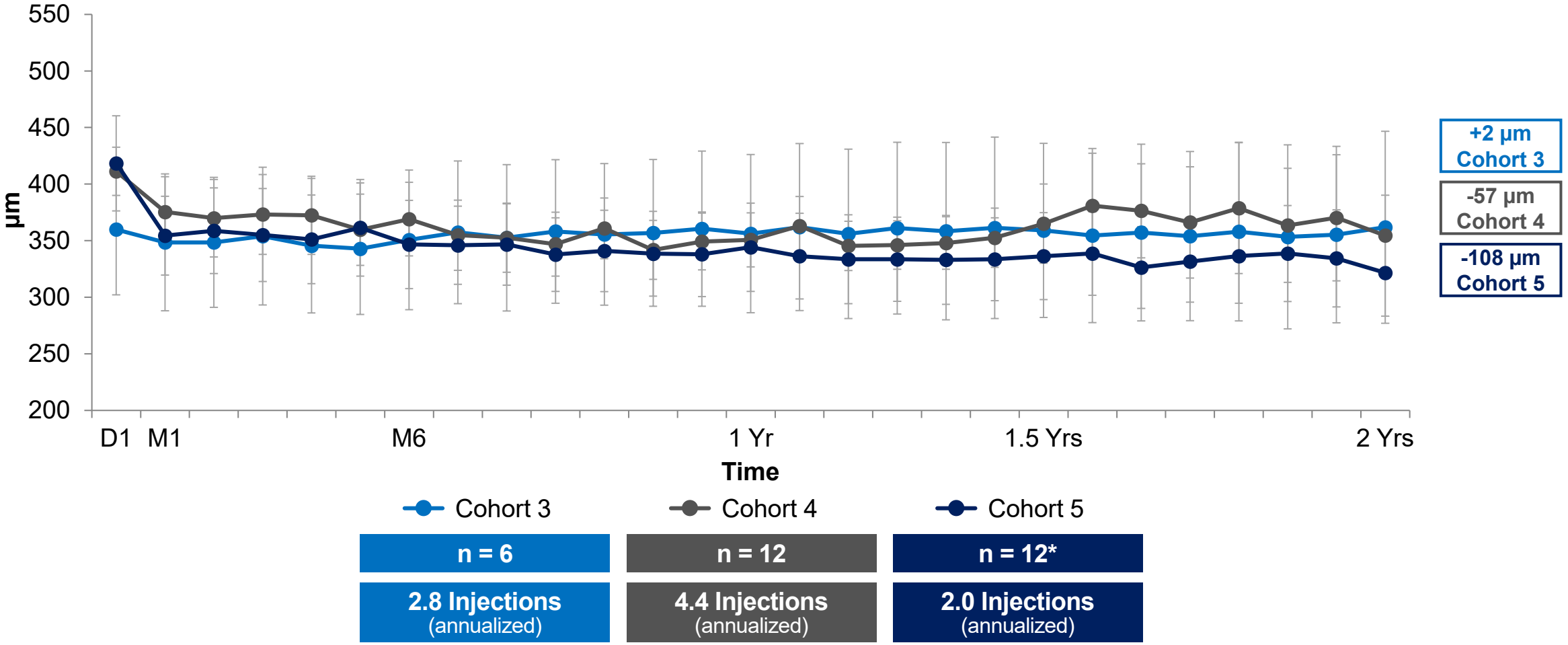
Central Retinal Thickness (CRT) by Central Reading Center



* One patient in Cohort 1 and one patient in Cohort 5 discontinued the study, both prior to visits at Week 22, 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). Fifteen additional missing CRT results were interpolated.

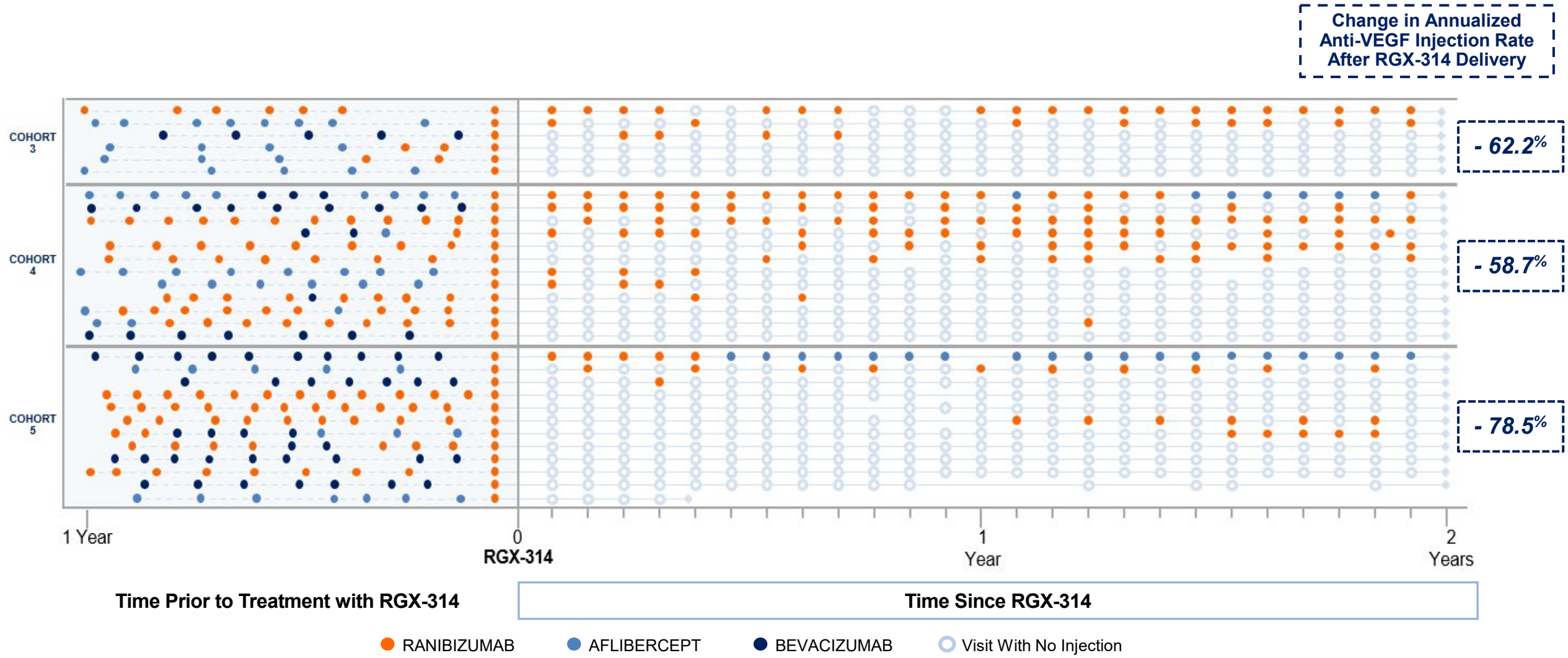
Mean CRT Over 2 Years in Cohorts 3-5

Central Retinal Thickness (CRT) by Central Reading Center

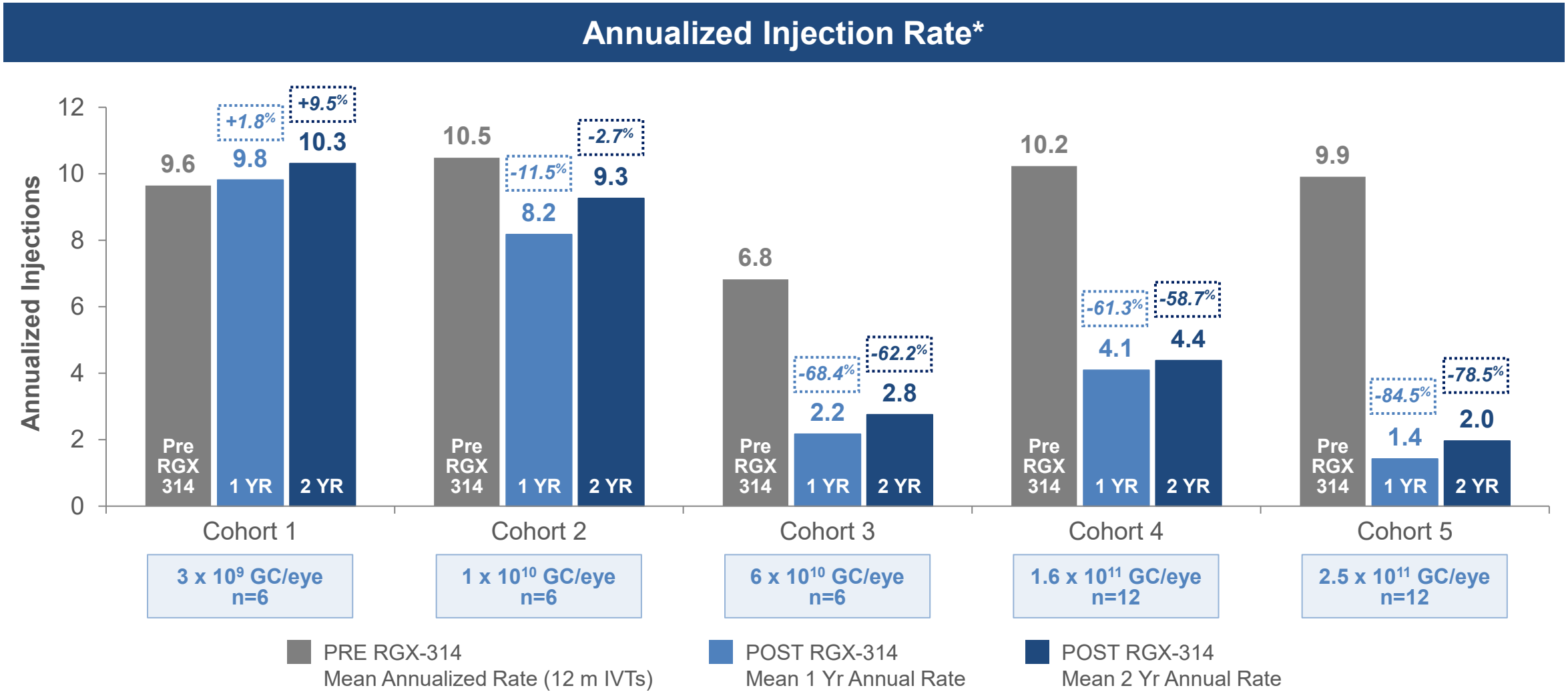


* One patient in Cohort 5 discontinued the study prior to the Week 22 visit and missing data post discontinuation was not imputed. Another patient in Cohort 5 has missed the visits due to COVID-19 from Week 50 through Week 74 and from Week 86 through Week 94. For this patient, missing visits were imputed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

Cohort 3-5 Injections PRE and POST RGX-314 Over 2 Years



Mean Change in Annualized Injection Rate PRE and POST RGX-314 in Cohorts 1-5



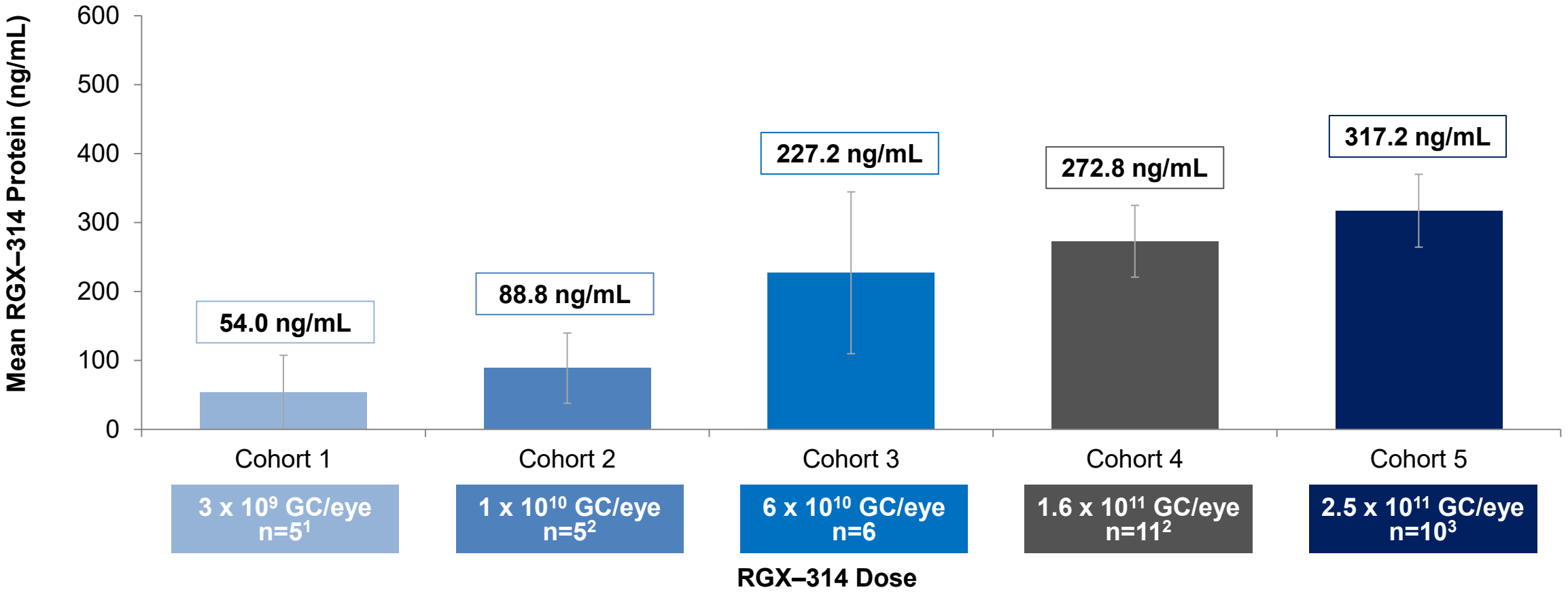
Retreatment Criteria: Any CNV-related increased, new, or persistent fluid; Vision loss of ≥5 letters associated with fluid; New ocular hemorrhage

* 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 First Pivotal Clinical Trial in nAMD

Key Objectives

Primary

- To evaluate mean change in **best corrected visual acuity** (BCVA) of RGX-314 relative to ranibizumab at Week 54

Secondary

- **Safety and tolerability** of RGX-314
- Mean change from baseline in Central Retinal Thickness (**CRT**) and Center Point Thickness (**CPT**) as measured by Spectral Domain Optical Coherence Tomography (SD-OCT)
- **Additional anti-VEGF injections** post-RGX-314
- Aqueous **RGX-314 protein** concentrations

Retreatment criteria

- Based on worsening vision and/or fluid

Subjects: 300 Patients

- **60 study sites** across the United States
- RGX-314 dosed **Subretinally**

Key Inclusion Criteria

- Male or female ≥ 50 to 89 years of age
- Diagnosis of subfoveal CNV secondary to AMD in the study eye **previously treated** with anti-VEGF
- BCVA: Between **40 and 78 ETDRS Letters** (20/32 to 20/160)
- Documented **response to anti-VEGF (ranibizumab) at trial entry**
- Pseudophakic
- Exclude any **subfoveal atrophy** or **fibrosis**

Conclusions from the RGX-314 Phase I/IIa Trial

RGX-314 remains generally well-tolerated in 42 patients with nAMD

- Patients are being followed in a Long-Term Follow-Up Study for an additional 3 years

Long-term, durable treatment effect demonstrated for Cohorts 3-5 over 2 years:

- Stable to improved visual acuity and retinal thickness
- Meaningful reductions in anti-VEGF injection burden

As previously presented, a long-term, durable treatment effect was demonstrated for Cohort 3 over 3 years[1]

- Improved visual acuity, with meaningful reductions in anti-VEGF injection burden

These results informed the study design of the pivotal program, to evaluate the efficacy and safety of RGX-314 in patients with nAMD

Data cut September 13, 2021

[1] Ho, AC. Angiogenesis, Exudation and Degeneration presentation, February 13, 2021