Suprachoroidal Delivery of RGX-314 for nAMD: AAVIATE® Study

10 | 3 | 2022

Agenda

- Welcome & Introductions
- Interim AAVIATE Study Update
- Q&A

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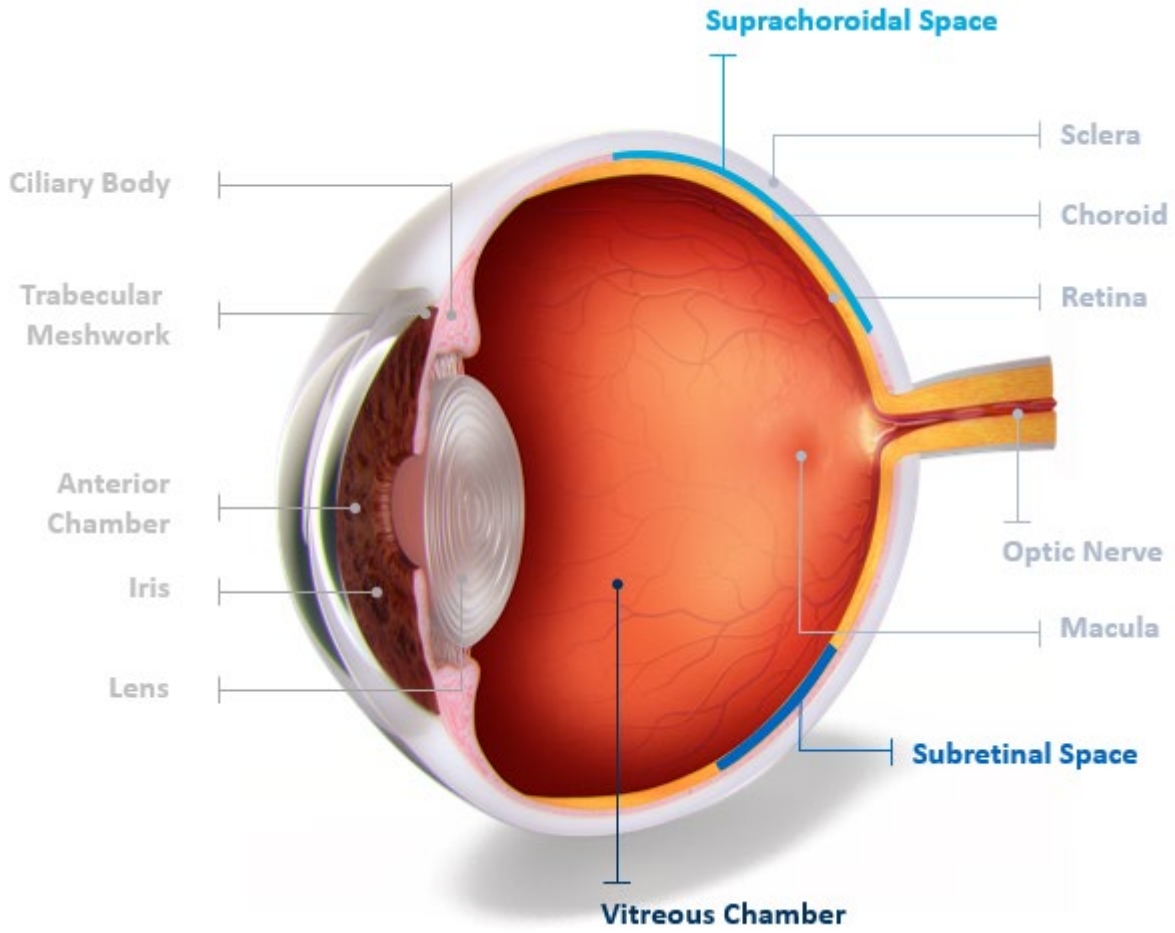
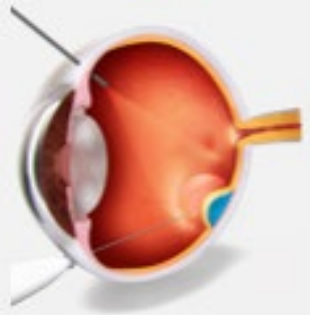
Ocular gene therapy delivery methods
Comparative profiles



Delivery Space Considerations

Suprachoroidal Space (SCS)[1]

- Targeted access and broad transduction of the retinal cells observed in preclinical studies
- Compartmentalized AAV delivery
- Minimal exposure to the vitreous and anterior segment



Subretinal Space[2,3]

- Targeted access and broad transduction of the retinal cells observed in preclinical studies
- Compartmentalized AAV delivery
- Minimal exposure to the vitreous and anterior segment
  - Low risk of immune response
  - Low risk of inflammation

Vitreous Chamber

- Inner limiting membrane (ILM) presents physical barrier, potentially limiting direct transduction of the retina[3]
  - Limited transduction of the retina observed in preclinical studies[4]
- Broad exposure to the vitreous and anterior segment
  - High risk of immune response[5,6]
  - High risk of inflammation[8]
  - Typically requires prophylactic corticosteroids[7]

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[1] Ding, K., et al. 2019 *Journal of Clinical Investigation*, [2] Vandenberghe et al. 2011 *Science Translational Medicine*, [3] Maclaren et al. 2016 *Lancet*, [4] Yin L, et al. 2011 *IOVS*, [5] Bennett, J., et al., 2017 *Human Gene Therapy*, [6] Heier JS, et al. 2016 *Lancet*, [7] Kotterman M, et al. 2015 *Gene Therapy*, [8] Bouquet C, et al. 2019 *JAMA Ophthalmology*

RGX–314 for Treatment of Neovascular Age-related Macular Degeneration (nAMD)

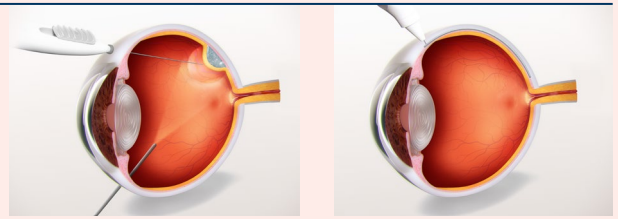
RGX–314 PRODUCT CANDIDATE

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

Route of administration:

Subretinal (nAMD) or

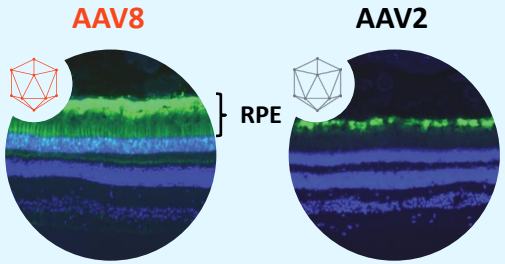
Suprachoroidal (nAMD/DR)



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
- **RGX–314 gene encodes an anti-VEGF mAb fragment (fab)**

=

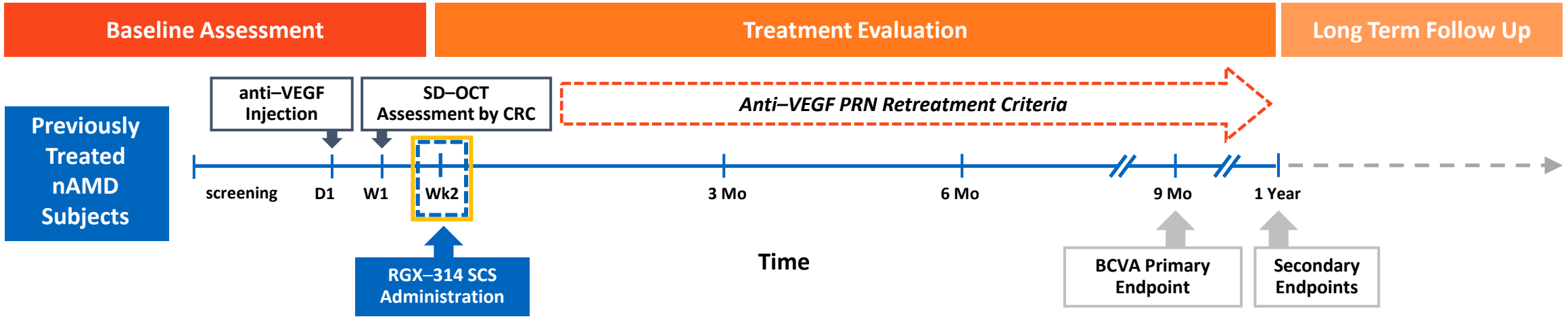
RGX–314: AAV8 encoding anti–VEGF fab

Potential for long-term therapeutic anti-VEGF expression

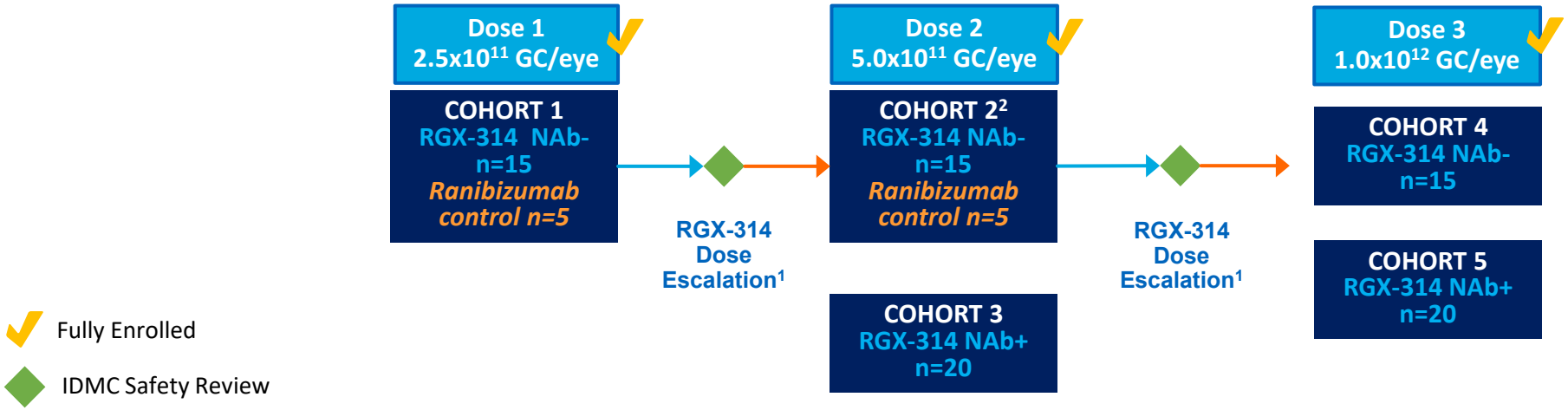
1. Vandenberghe et al. 2011 Science Translational Medicine.

AAV: Adeno-Associated Virus

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.
2. Subjects in Cohort 2 received two doses of 100µL, all other cohorts received one dose of 100µL.

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

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

Primary Objective

- To evaluate the mean change in BCVA for RGX-314 compared with ranibizumab monthly injection at Month 9

Secondary Objectives

- Safety and tolerability of RGX-314
- Change in central retinal thickness (CRT) as measured by Spectral Domain Optical Coherence Tomography (SD-OCT)
- Additional anti-VEGF injections post-RGX-314 (“Rescue”)

Retreatment Criteria

- Based on worsening vision and/or fluid

Subjects: 95 patients enrolled

- **15 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 ≥ 50 to 89 years of age
- Previously treated nAMD subjects with fluid on OCT at trial entry
- Documented response to anti–VEGF at trial entry (assessed by Reading Center)
- BCVA between ≤ 20/25 and ≥ 20/125 (≤ 83 and ≥ 44 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) in the study eye
- Phakic or Pseudophakic

AAVIATE Baseline Characteristics (Cohort 1 to 5)

	Variable	Control Ranibizumab (N=10)	Cohort 1 Dose 1 NAb- (N=15)	Cohort 2 Dose 2 NAb- (N=15)	Cohort 3 Dose 2 NAb+ (N=20)	Cohort 4 Dose 3 NAb- (N=15)	Cohort 5 Dose 3 NAb+ (N=20)	Total (N=95)
BASELINE	**Mean Age** (Years)	75.9	74.0	77.9	72.6	79.7	75.0	75.6
	Screening BCVA (Letters)	72.7	75.1	70.7	72.8	73.1	73.4	73.0
	Screening OCT (Microns)	240.3	269.2	275.7	265.8	256.9	271.0	264.9
	Phakic n (%)	3(30.0%)	6 (40.0%)	7 (46.7%)	10 (50.0%)	4 (26.7%)	10 (50.0%)	40 (42.1%)
PRIOR THERAPY	**Months Since nAMD Diagnosis** (Mean)	26.7	30.4	19.9	18.6	23.5	22.4	23.1
	# Injections Since nAMD Diagnosis (Mean)	13.4	20.6	11.1	9.7	16.4	13.4	13.8
	# Injections in the Past Year (includes Day 1)	6.8	7.2	6.0	6.2	7.1	6.5	6.6
	Average Annualized Injections in the Past Year (includes Day 1)	8.8	9.7	8.7	8.9	9.3	9.5	9.2

Average annualized injections in the past year is: (Total # of prior injections)/(minimum(366 days, Duration between first injection and Day 1)/365.25). NAb+ = AAV8 neutralizing antibody positive; NAb- = AAV8 neutralizing antibody negative/low

AAVIATE® Safety Summary

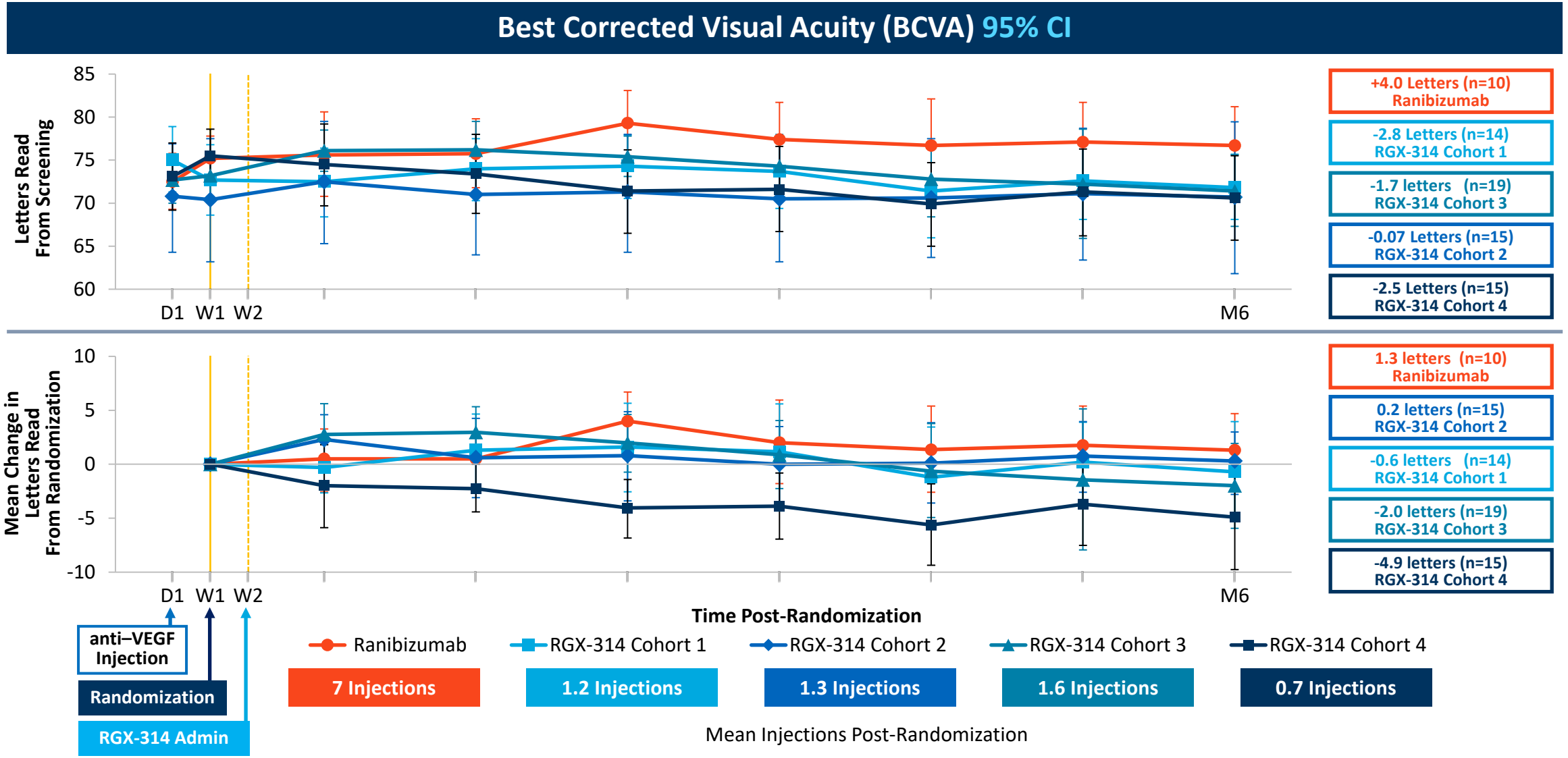
- RGX–314 was well–tolerated in Cohorts 1–5 (n=85) with follow-up ranging from 1–12 months post dosing
  - 15 SAEs: None considered drug-related
  - No cases of chorioretinal vasculitis or occlusion, or hypotony were observed

Cohort 1 to 4: Common Ocular TEAEs[1] 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)	Cohort 4 Dose 3 NAb - (N=15)	Total (N=65)
Intraocular Inflammation[2]	4 (26.7%)	3 (20.0%)	2 (10.0%)	6 (40.0%)	15 (23.1.%)
Conjunctival Hemorrhage	5 (33.3%)	2 (13.3%)	3 (15.0%)	1 (6.7%)	11 (16.9%)
Intraocular Pressure Increased[3]	1 (6.7%)	2 (13.3%)	3 (15.0%)	3 (15.0%)	9 (13.8%)
Conjunctival Hyperemia	2 (13.3%)	1 (6.7%)	1 (5.0%)	3 (20.0%)	7 (10.8%)
Episcleritis[4]	0	3 (20.0%)	2 (10.0%)	2 (13.3%)	7 (10.8%)

No meaningful differences based on **baseline AAV8 NAbs**

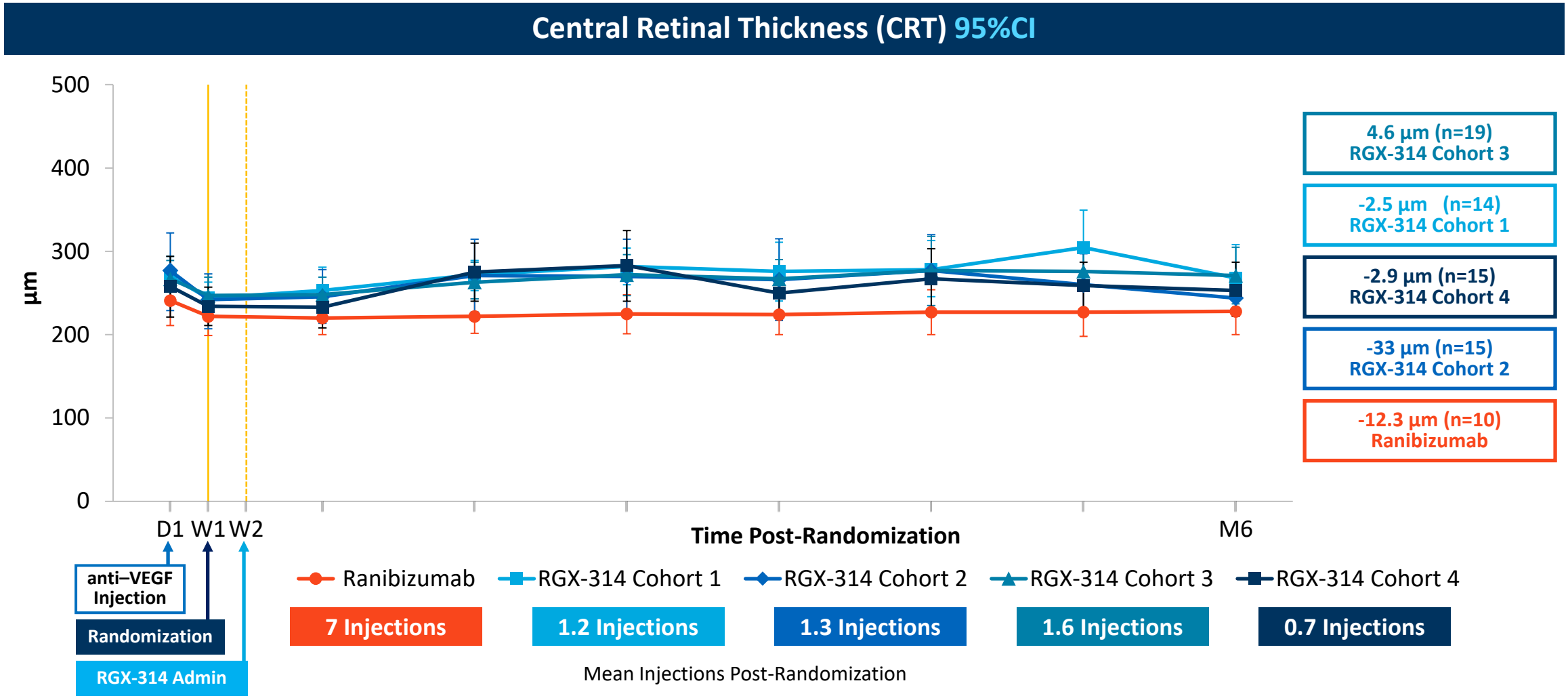
Data cut: August 01, 2022.
1. Includes AEs for total group ≥10% with onset up to 6m visit.
2. All cases were mild to moderate (range +0.5 to 2+), most presented 2-6 weeks post injection, predominantly as anterior cells on slit lamp examination. Resolved on topical corticosteroids.
3. Intraocular pressure increased and ocular hypertension have been combined into one group. All mild to moderate and all controlled.
4. All mild (grade 1), presented 2-6 weeks post injection and resolved on topical corticosteroid or NSAID treatment.

Cohorts 1-4: Mean BCVA Through Month 6



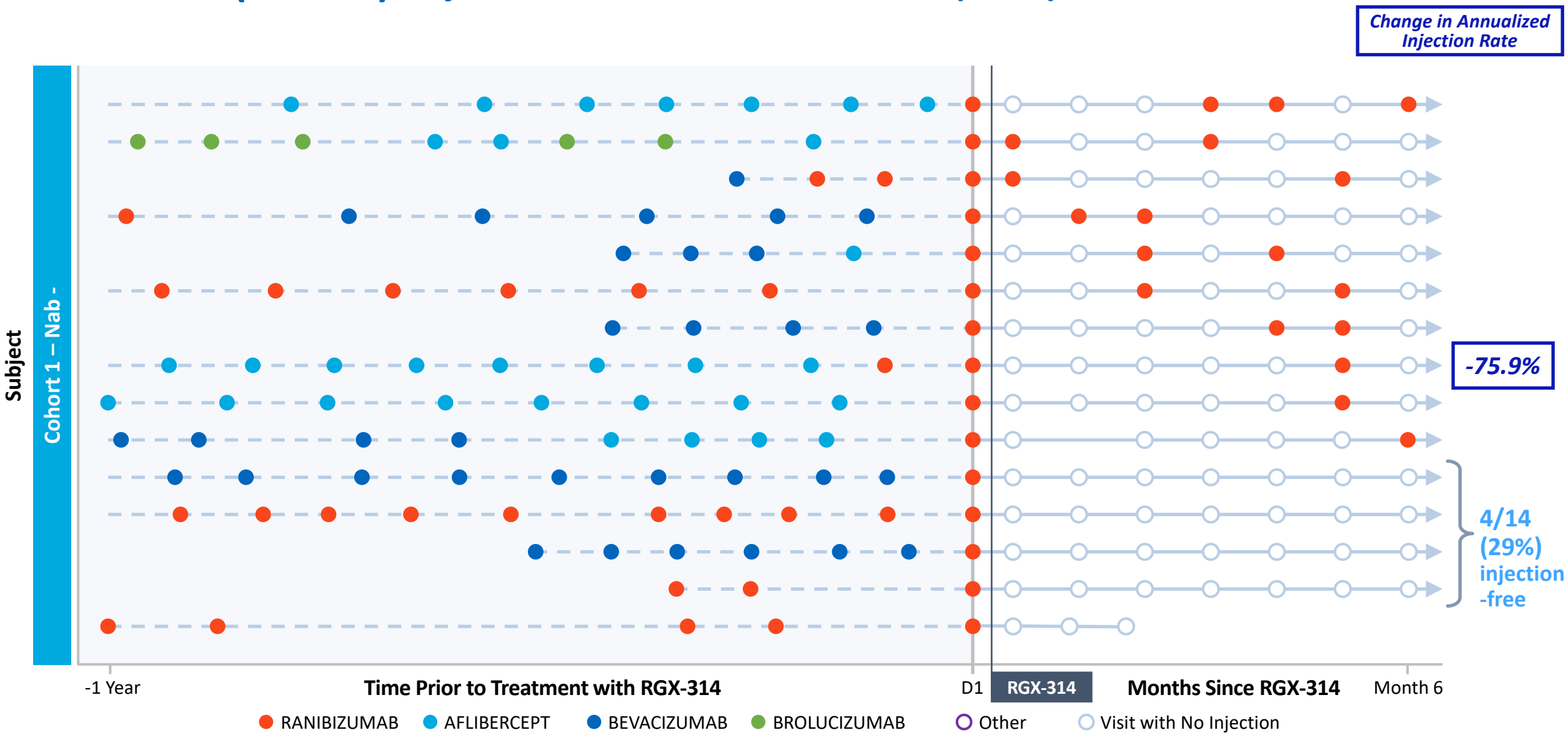
Data cut: August 1, 2022.

Cohorts 1–4: Mean CRT from Day 1 (Screening) Through Month 6



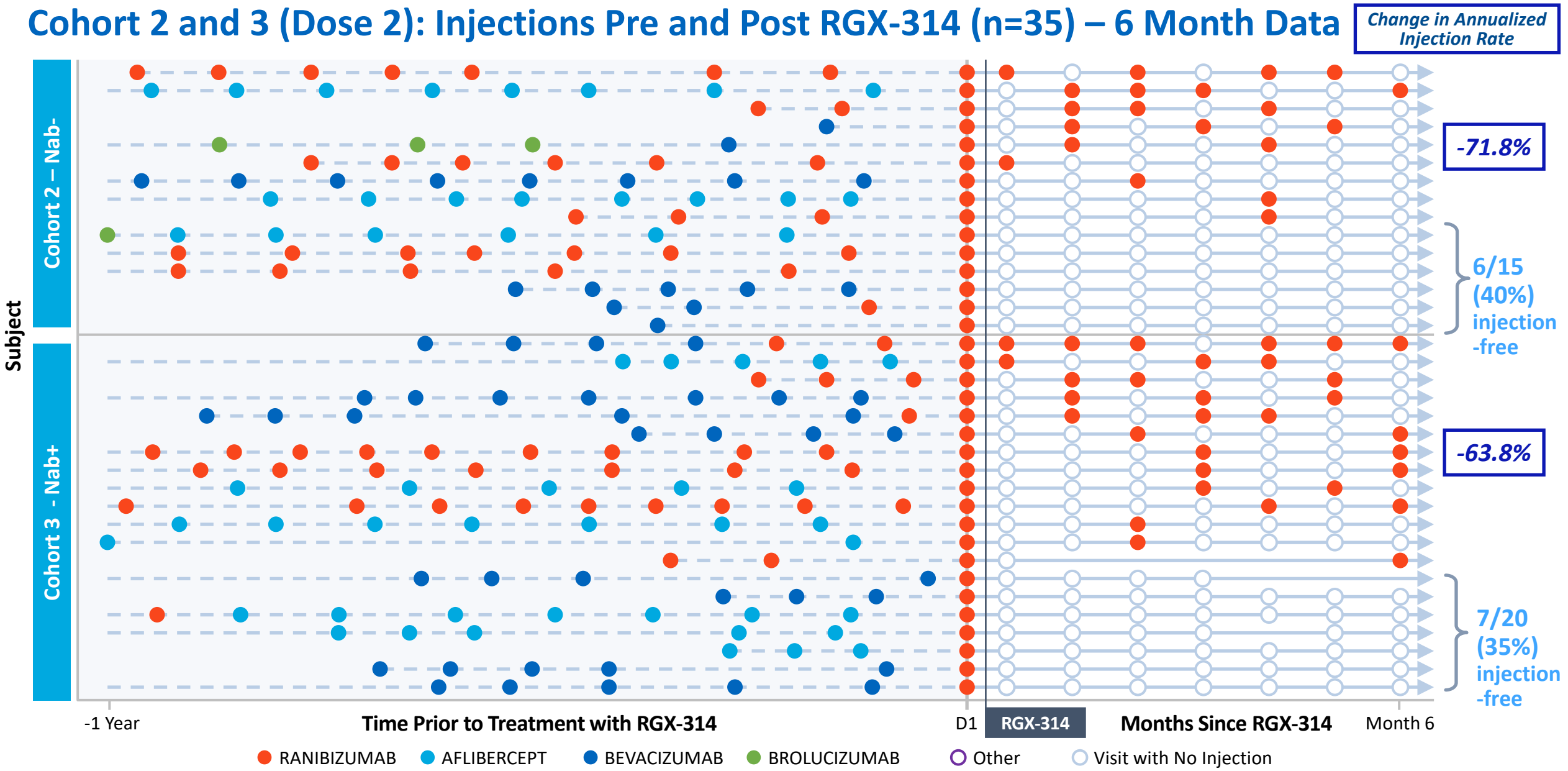
Data cut: August 1, 2022.

Cohort 1 (Dose 1): Injections Pre and Post RGX-314 (n=15) – 6 Month Data



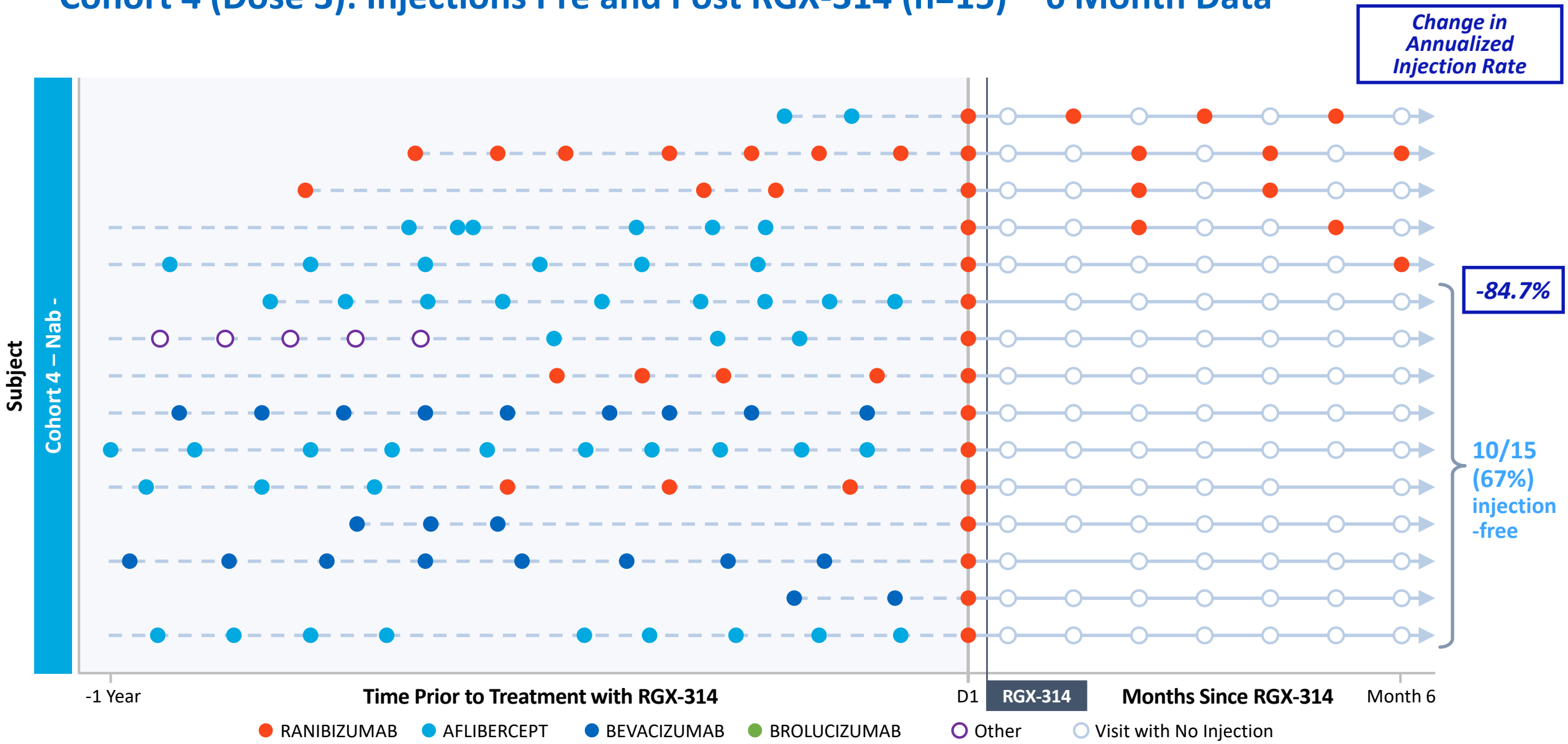
Data cut: August 1, 2022.

Cohort 2 and 3 (Dose 2): Injections Pre and Post RGX-314 (n=35) – 6 Month Data



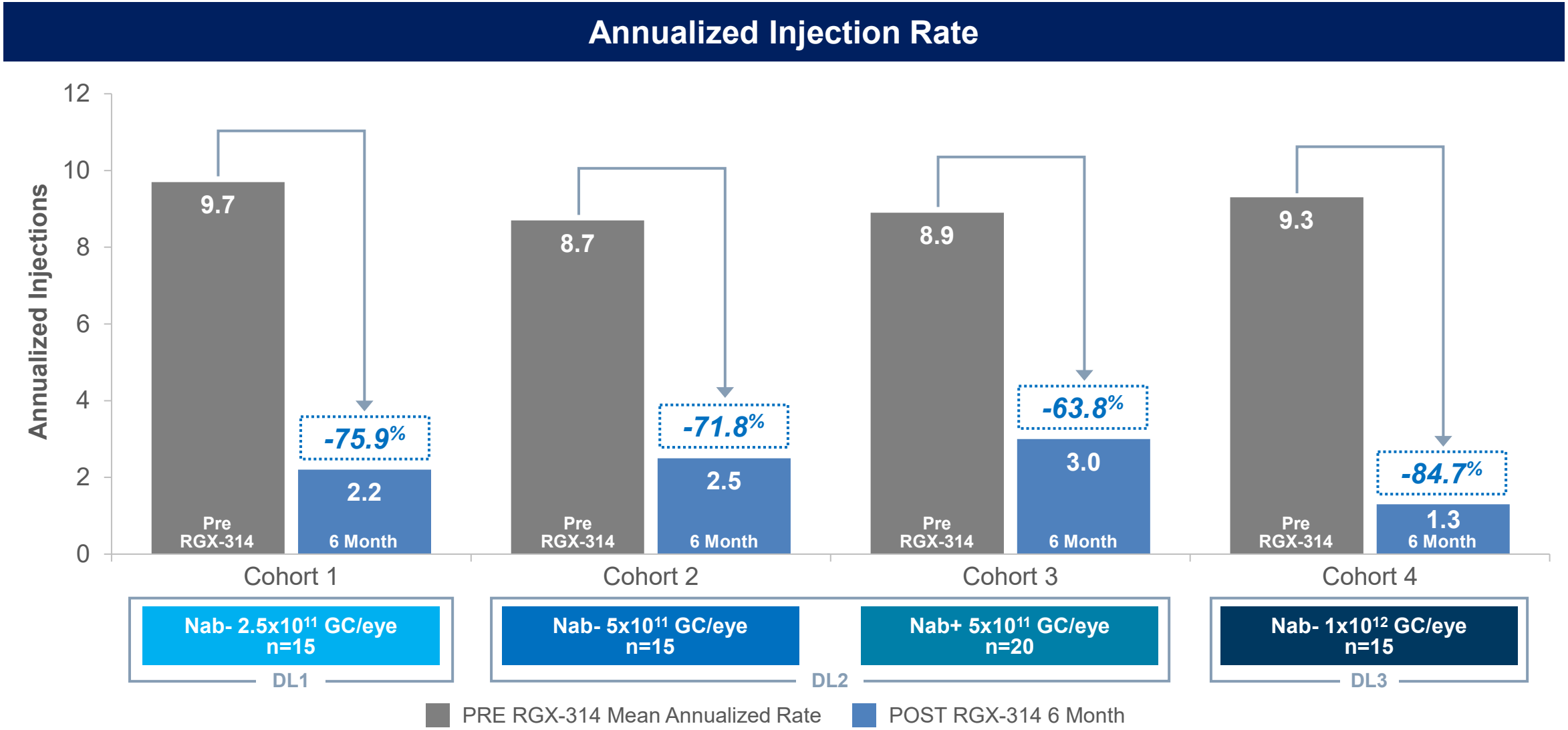
Data cut: August 1, 2022.

Cohort 4 (Dose 3): Injections Pre and Post RGX-314 (n=15) – 6 Month Data



Data cut: August 1, 2022.

Mean Change in Annualized Injection Rate PRE and POST RGX-314 in Cohorts 1–4

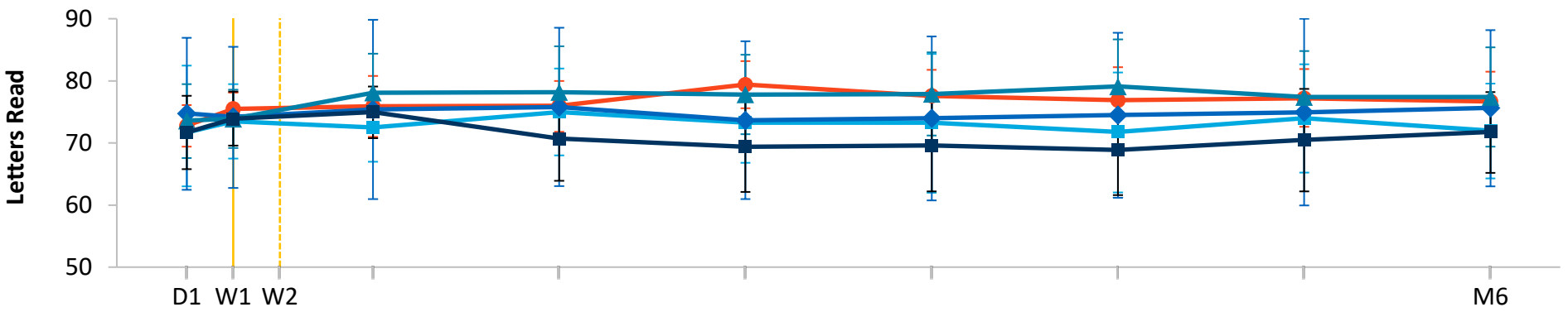


Data cut: August 1, 2022.

Cohorts 1-4: Subjects with No Anti-VEGF Injections over 6 Months

Mean BCVA and CRT from Day 1 (Screening)

Best Corrected Visual Acuity (BCVA) 95% CI



+1.0 letters (n=6)
RGX-314 Cohort 2

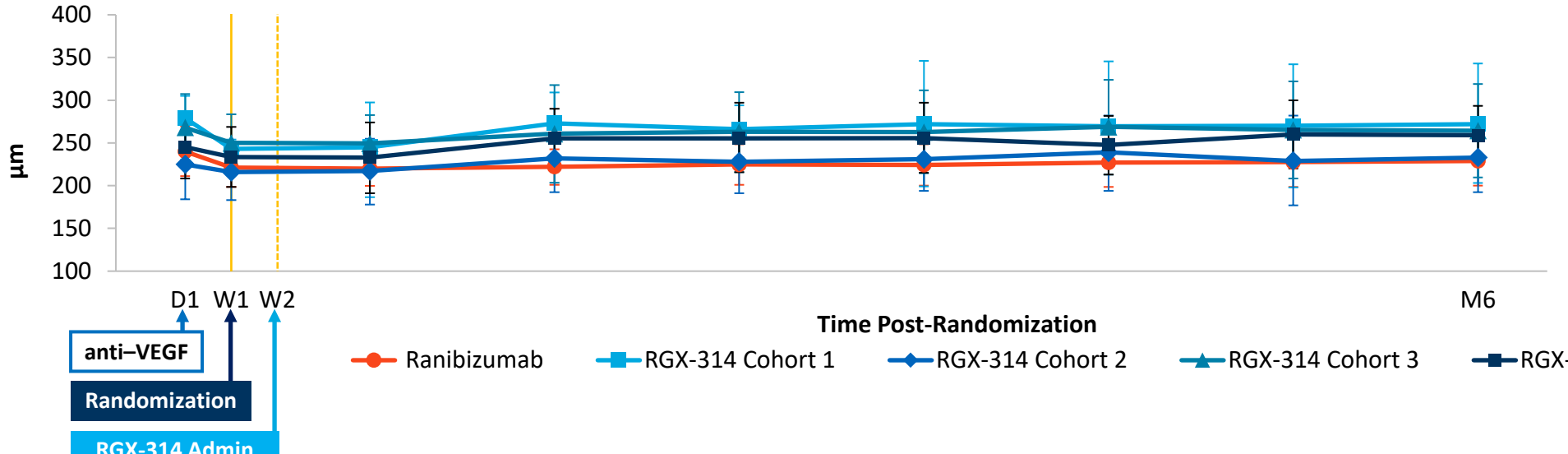
+4.0 Letters (n=10)
Ranibizumab

+2.3 letters (n=6)
RGX-314 Cohort 3

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

0 letters (n=10)
RGX-314 Cohort 4

Central Retinal Thickness (CRT) 95% CI



-5.8 µm (n=4)
RGX-314 Cohort 1

-4.0 µm (n=6)
RGX-314 Cohort 3

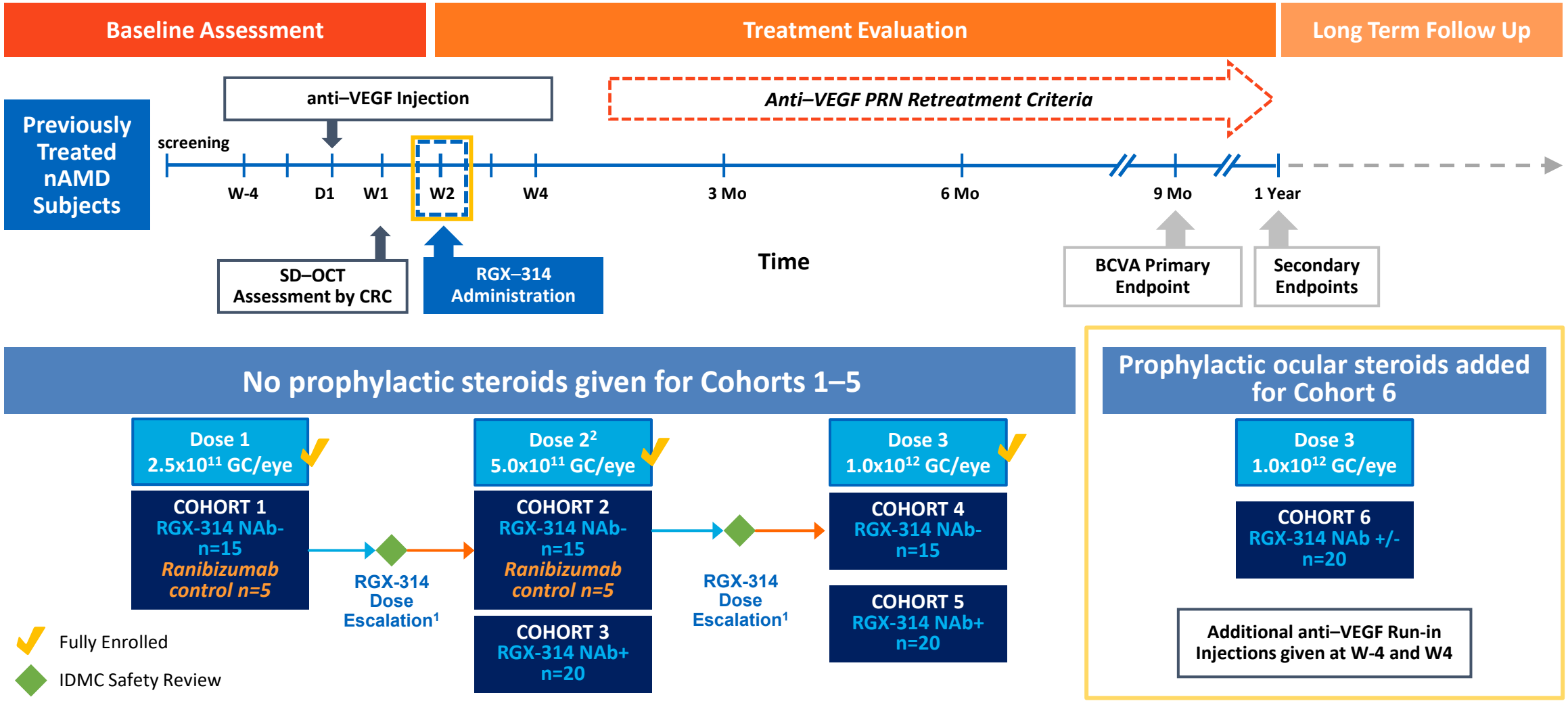
+13.7 µm (n=10)
RGX-314 Cohort 4

+7.5 µm (n=6)
RGX-314 Cohort 2

-12.3 µm (n=10)
Ranibizumab

Data cut: August 1, 2022.

AAVIATE®: Study Design with Addition of Cohort 6



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NAb+ = AAV8 neutralizing antibody positive; NAb- = AAV8 neutralizing antibody negative/low

Summary of Results from the Phase II AAVIATE® nAMD Study

RGX-314 Cohorts 1-5 (n=85): Safety

- Suprachoroidal RGX-314 has been well-tolerated

RGX-314 Cohorts 1-4 (n=65): 6 Month Results

- RGX-314 treated patients had **stable vision and retinal thickness,** with a **meaningful reduction in treatment burden** across all dose levels; **highest reduction in treatment burden seen in Cohort 4 (Dose 3):**
  - 85% reduction in annualized injection rate
  - 67% injection-free
- No meaningful differences in patient outcomes with and without **baseline AAV8 NAbs**
- Intraocular inflammation (IOI) resolved with topical corticosteroids
  - **Cohorts 1–3 (Dose 1 and 2)** - all mild and similar incidence observed across doses
  - **Cohort 4 (Dose 3)** - mild to moderate with increased incidence compared to prior doses

AAVIATE is currently enrolling a new Cohort 6 to further evaluate Dose 3 ($1x10^{12}$ GC/eye) with short-course, ocular steroids following RGX-314

Data cut: August 01, 2022.

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Thank You