Suprachoroidal Therapy for Neovascular AMD

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Disclosures

AbbVie Inc[C]

Adverum Biotech[CR]

Alcon[C]

Alimera[C]

Allegro[C]

Allergan[C]

Annexon Biosciences[R]

Apellis[B]

Arctic Vision[C]

Bausch and Lomb[C]

Biogen[C]

Clearside Biomedical[CR]

Coherus Biosciences[C]

EyePoint Pharma[CR]

Gemini Therapeutics[R]

Genentech[BCR]

Graybug[CR]

Gyroscope Therapeutics[R]

Kodiak Sciences[CR]

Novartis[BCR]

NeuBase[E]

Ocular Therapeutix[C]

Oculis[R]

Opthea[CR]

Outlook Therapeutics[C]

Oxular[R]

Oxurion[ER]

Palatin Technologies[C]

Regeneron[B]

RegenxBio[CR]

ReNeuron[R]

RevOpsis Therapeutics[CE]

Ribomic[R]

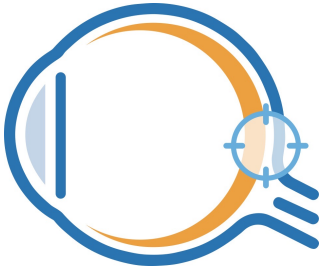
Roche[C]

Stealth Biotherapeutics[R]

Unity Biotechnology[R]

B = Speakers' Bureau; C = Consultant; E = Equity; R = Research

Why Suprachoroidal Space?



TARGETED

for efficacy

The back of the eye is the location of many irreversible and debilitating visual impairments

COMPARTMENTALIZED

for safety

Drug is compartmentalized in the suprachoroidal space, which helps keep it away from non-diseased tissues and entirely behind the visual field

BIOAVAILABLE & PROLONGED DRUG LEVELS

for durability

Fluid spreads circumferentially and posteriorly when injected within the suprachoroidal space, bathing the choroid and adjacent areas with drug

Sources: Rai UDJ, Young SA, Thrimawithana TR, et al. The suprachoroidal pathway: a new drug delivery route to the back of the eye. Drug Discov Today. 2015;20(4):491-495. | Moisseiev E, Loewenstein A, Yiu G. The suprachoroidal space: from potential space to a space with potential. Clin Ophthalmol. 2016;10:173-178. | Chiang B, Jung JH, Prausnitz MR. The suprachoroidal space as a route of administration to the posterior segment of the eye. Adv Drug Deliv Rev. 2018;126:58-66.

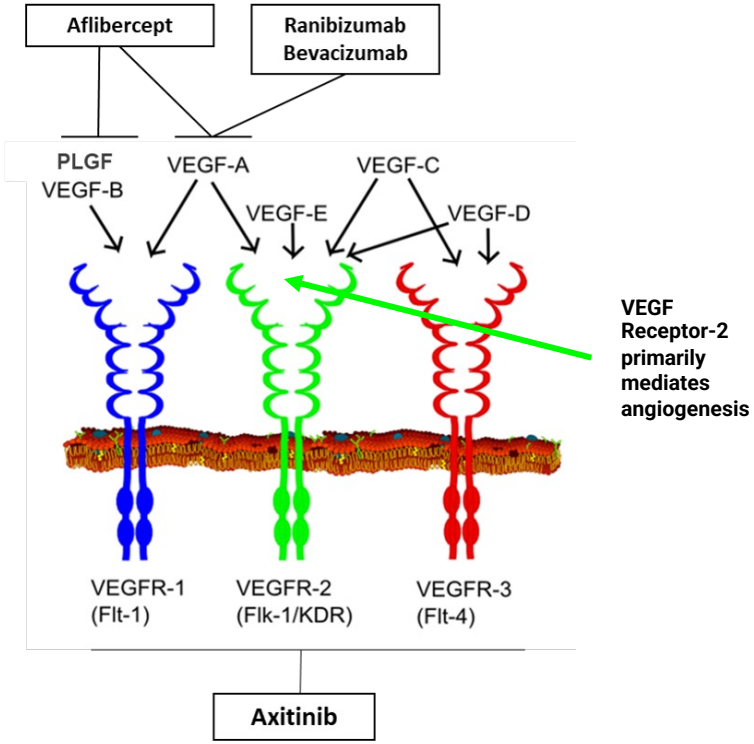
CLS-AX

(axitinib injectable suspension)

for Suprachoroidal Injection

Axitinib: a Highly Potent, Pan-VEGF TKI to Treat Wet AMD

- Axitinib's intrinsic pan-VEGF inhibition through receptor blockade
  - Approved treatments are focused VEGF-A inhibitors
- Inhibits **VEGFR-1**, **VEGFR-2**, **VEGFR-3** receptors
  - More active than anti-VEGF-A in *in-vitro* angiogenesis model[1-2]
- Highly potent tyrosine kinase inhibitor (TKI)
  - >10x more potent than other TKIs in preclinical studies
  - Better ocular cell biocompatibility than other TKIs[3]
  - More active than other TKIs for experimental corneal neovascularization in preclinical models
- Preclinical data showed axitinib inhibition and regression of angiogenesis

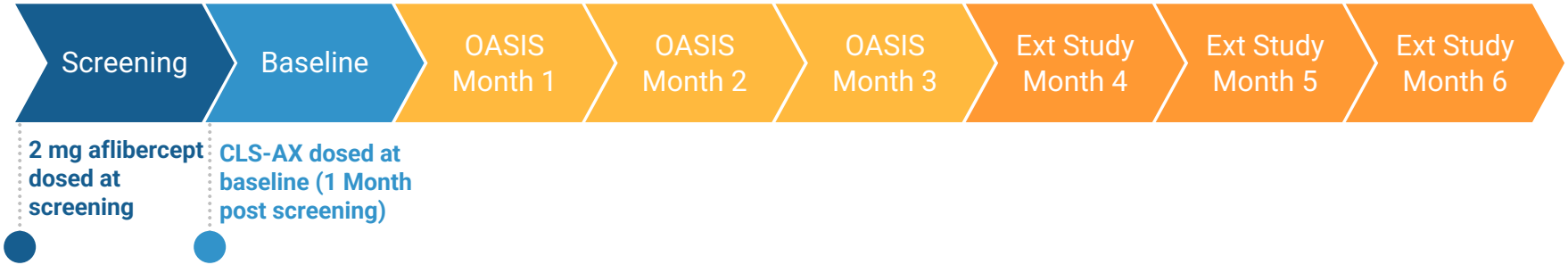


Sources: 1. Cabral T et al. Bevacizumab Injection in Patients with Neovascular Age-Related Macular Degeneration Increases Angiogenic Biomarkers. Ophthalmol Retina. 2018 January ; 2(1): 31–37. doi:10.1016/j.oret.2017.04.004. | 2. Lieu et al. The Association of Alternate VEGF Ligands with Resistance to Anti-VEGF Therapy in Metastatic Colorectal Cancer. PLoS ONE 8(10): e77117. | 3. Theile et al. Multikinase Inhibitors as a New Approach in Neovascular Age-Related Macular Degeneration (AMD) Treatment: In Vitro Safety Evaluations of Axitinib, Pazopanib and Sorafenib for Intraocular Use. Klin Monatsbl Augenheilkd 2013; 230: 247-254. | Image by Mikael Häggström, used with permission. Häggström, Mikael (2014). "Medical gallery of Mikael Häggström 2014". WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.008. ISSN 2002-4436. Public Domain.

OASIS and Extension Study: CLS-AX Phase 1/2a Clinical Trial in Treatment-Experienced Wet AMD Patients with Active Disease at Screening

TRIAL DESIGN AND OBJECTIVES

- Open-label study with a primary endpoint to evaluate safety and tolerability of escalating single doses of CLS-AX administered through suprachoroidal injection following IVT aflibercept
- Wet AMD patients with ≥2 anti-VEGF treatments in the prior 4 months, reading center confirmation of persistent active disease
- Dose-escalation of CLS-AX (in mg): Cohort 1 at 0.03; Cohort 2 at 0.1; Cohort 3 at 0.5; Cohort 4 at 1.0
- Secondary endpoints: visual function, ocular anatomy, and need for additional treatment
- Monthly assessment for additional treatment with aflibercept: loss from best measurement of ≥10 letters in BCVA with exudation; increase in CST >75 microns; a vision-threatening hemorrhage
- 6-Month follow-up after CLS-AX via a 3-month Extension Study



Note: aflibercept is dosed via intravitreal injection (IVT); CLS-AX is dosed via suprachoroidal injection | clinicaltrials.gov NCT# 04626128

Active Disease definition: Active subfoveal choroidal neovascularization (CNV) secondary to AMD in the study eye confirmed by an independent reading center as leakage from a subfoveal CNV on fluorescein angiography and intra-retinal or sub-retinal fluid on OCT central subfield)

Enrolled Patients All with Active Disease at Screening and Confirmed by Independent Reading Center

Demographics and Wet AMD History

Wet AMD Disease Characteristics	COHORT 1: 0.03 mg	COHORT 2: 0.1 mg	COHORT 3: 0.5 mg	COHORT 4: 1.0 mg
No. of participants	6	5	8	8
Mean age (range), years	81.8 (66-93)	78.2 (65-90)	86.3 (75-97)	76.5 (66-83)
Mean baseline best corrected visual acuity (range), letters	59.0 (29-74)	65.6 (52-75)	58.5 (37-74)	65.8 (50-74)
Mean baseline central subfield retinal thickness (range), µm	231.2 (208-294)	209.4 (184-227)	202.0 (175-238)	218.8 (152-295)
Mean duration of wAMD diagnosis (range), months	**50.13 (12.4-110.3)**	**49.78 (24.7-81.3)**	**66.64 (6.8-102.1)**	**48.21 (4.5-132.8)**
Number of anti-VEGF injections reported prior to CLS-AX administration on Day 1, mean (range)	**26.8 (7-41)**	**24.2 (12-39)**	**37.0 (6-90)**	**28.8 (5-89)**
Annualized number of anti-VEGF injections prior to CLS-AX administration on Day 1, mean (range)	**9.36 (6.3-12.7)**	**9.54 (5.4-12.2)**	**8.47 (4.9-11.8)**	**11.96 (8.9-13.6)**

Source: Clearside data on file.

Extension Study: Demographics and Wet AMD History

Wet AMD Disease Characteristics	COHORT 2: 0.1 mg	COHORT 3: 0.5 mg	COHORT 4: 1.0 mg	Total
No. of participants	2	7	5	14
Mean age (range), years	74.0 (70-78)	87.9 (81-97)	79.6 (74-83)	82.9 (70-97)
Mean baseline best corrected visual acuity (range), letters	60.0 (52-68)	59.0 (37-74)	71.2 (69-74)	63.5 (37-74)
Mean baseline central subfield retinal thickness (range), µm	213.5 (200-227)	201.9 (175-238)	214.8 (197-234)	208.1 (175-238)
Mean duration of wAMD diagnosis (range), months	**44.30 (33.9-54.7)**	**67.29 (6.8-102.1)**	**36.42 (6.1-103.4)**	**52.98 (6.1-103.4)**
Number of anti-VEGF injections reported prior to CLS-AX administration on Day 1, mean (range)	**23.0 (12-34)**	**38.9 (6-90)**	**33.2 (6-89)**	**34.6 (6-90)**
Annualized number of anti-VEGF injections prior to Enrollment, mean (range)	**8.81 (5.4-12.2)**	**8.84 (4.9-11.9)**	**12.01 (10.5-13.1)**	**9.97 (4.9-13.1)**

Source: Clearside data on file.
Cohort 2 data calculated with number of patients with available data. Cohorts 3 & 4 data calculated with number of participants.

OASIS RESULTS: 6-month final

CLS-AX Demonstrated a Positive Safety Profile in All Four Cohorts

3-Month & 6-Month Extension Study Data

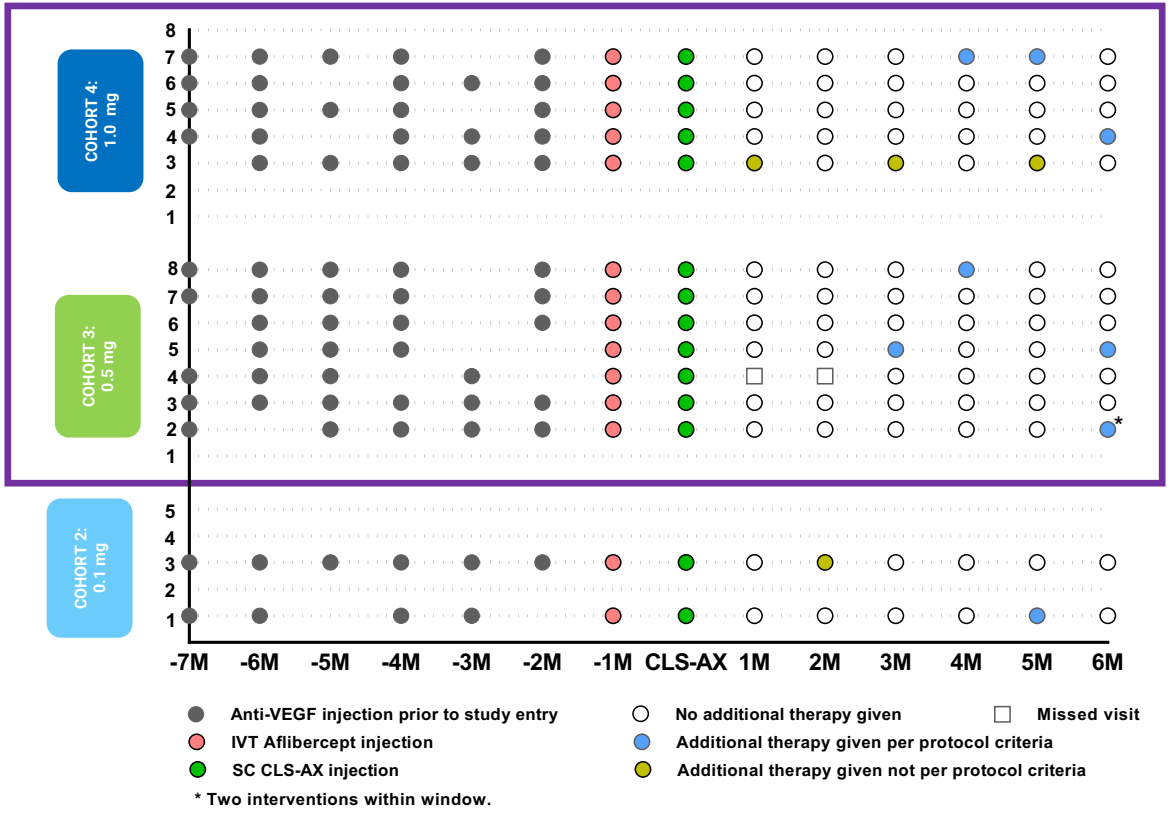
SAFETY DATA

Excellent Safety Profile at all doses and timepoints

- No serious adverse events (SAEs)
- No treatment emergent adverse events (TEAEs) related to study treatment
- No dose limiting toxicities
- No adverse events related to inflammation, vasculitis or vascular occlusion
- No vitreous “floaters” or dispersion of CLS-AX into the vitreous
- No retinal detachment
- No endophthalmitis
- No adverse events related to intraocular pressure

Source: Clearside data on file.

Extension Study (6 Month Data): Prior Anti-VEGF Therapies and All Additional Therapies



DURABILITY

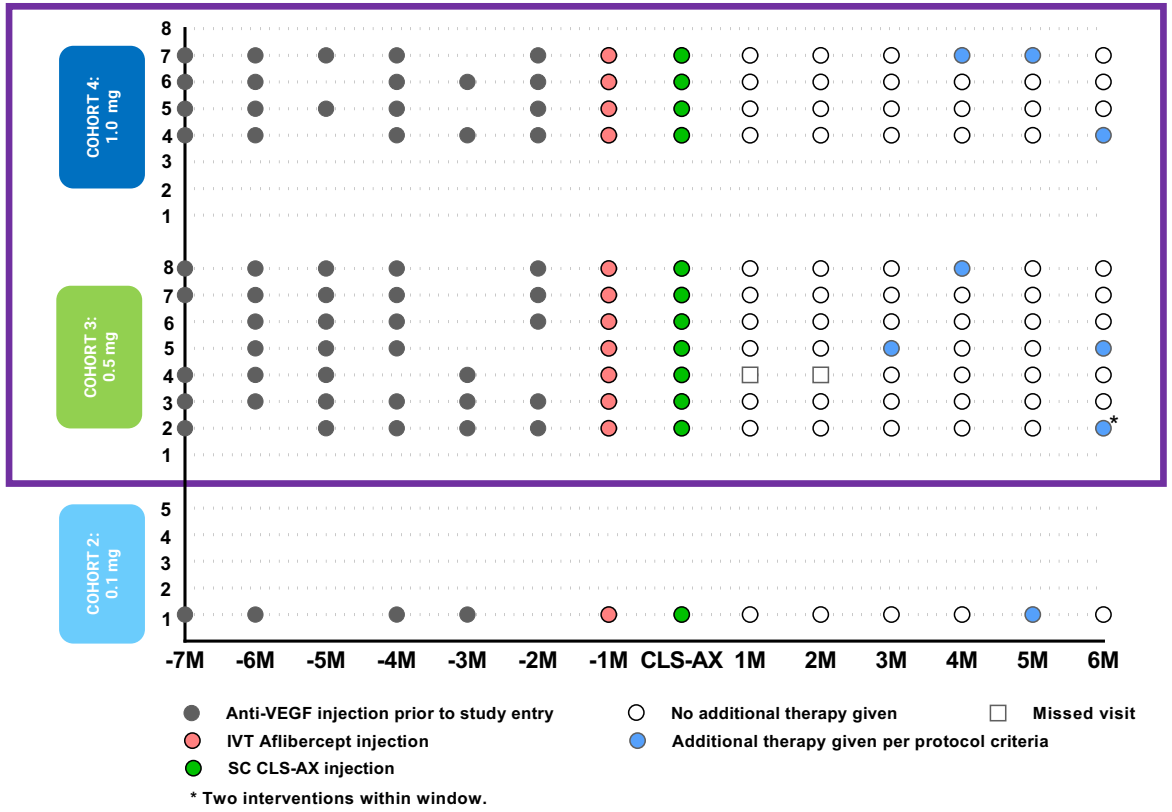
Cohorts 3 & 4

No Additional Therapy

- ≥ 3 Months: 11/12 (92%)
- ≥ 4 Months: 10/12 (83%)
- ≥ 6 Months: 8/12 (67%)
- > 6 Months: 6/12 (50%)

Source: Clearside data on file.

Extension Study (6 Month Data): Prior Anti-VEGF Therapies and Additional Therapies Per Protocol Criteria



DURABILITY

Cohorts 3 & 4

No Additional Therapy

≥ 3 Months: 11/11 (100%)
≥ 4 Months: 10/11 (91%)
≥ 6 Months: 8/11 (73%)
> 6 Months: 6/11 (55%)

Excludes patients whose first additional therapy was not per protocol-defined criteria.
Source: Clearside data on file.

Extension Study (6 Month): CLS-AX Demonstrated Reduction of Treatment Burden Across Cohorts

Observed Reduction in Treatment Burden
All Therapies

Cohort	Number of Participants	Avg Monthly Injections Before CLS-AX Administration	Avg Monthly Injections After CLS-AX Administration	% Reduction
4	5	0.87	0.20	**77.0**
3	7	0.81	0.12	**85.2**
2	2	0.83	0.17	79.5

Observed Reduction in Treatment Burden
Therapies Per Protocol Criteria

Cohort	Number of Participants	Avg Monthly Injections Before CLS-AX Administration	Avg Monthly Injections After CLS-AX Administration	% Reduction
4	4	0.83	0.13	**84.3**
3	7	0.81	0.12	**85.2**
2	1	0.67	0.17	74.6

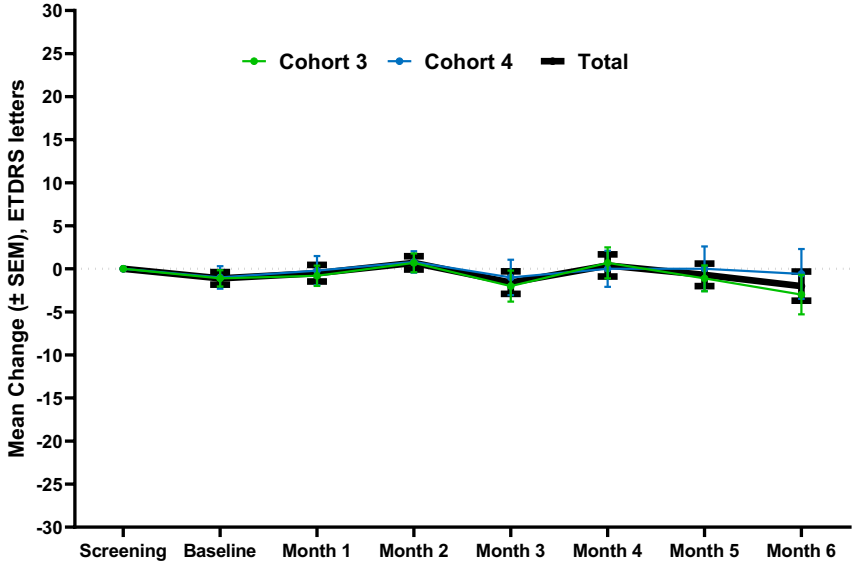
77 – 85% Reduction in Treatment Burden in Cohorts 3 and 4

Note: Average Monthly Injections Before CLS-AX Administration = # treatments six months prior/ 6.
Average Monthly Injections After CLS-AX Administration = # treatments / # months of follow-up.
% Reduction = Average of individual reductions calculated as (after – before) / before × 100%.
Source: Clearside data on file.

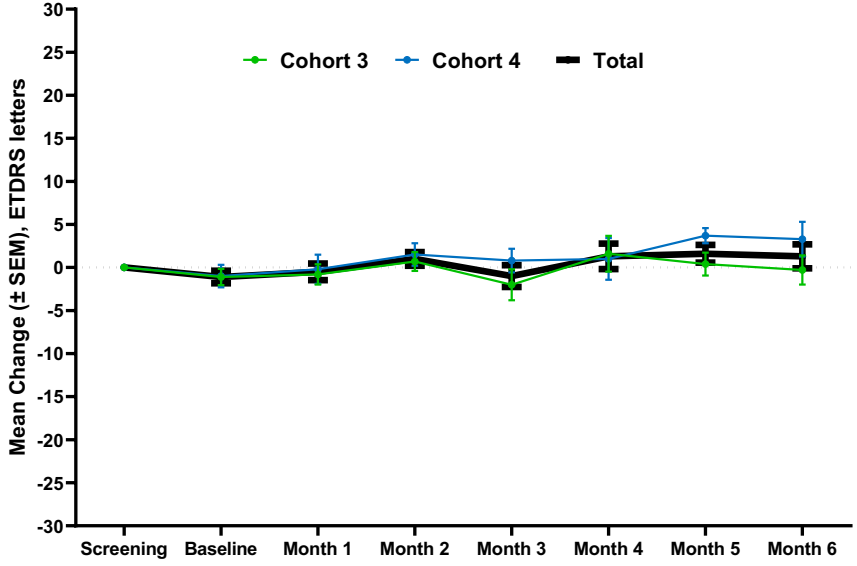
Extension Study (6 Month): Stable Visual Acuity

Mean Best Corrected Visual Acuity Letter Score, Change from Screening

All Data



Excluding Data After Additional Treatment

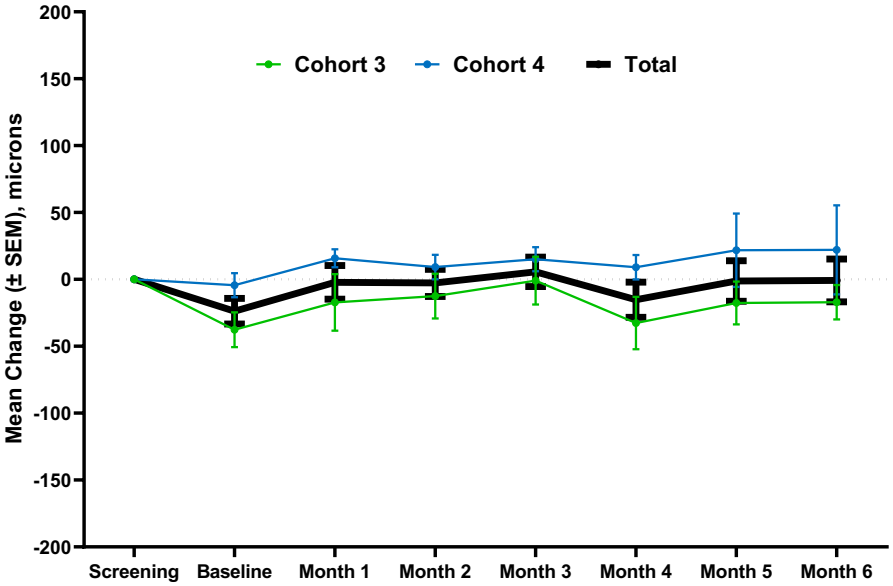


Source: Clearside data on file.

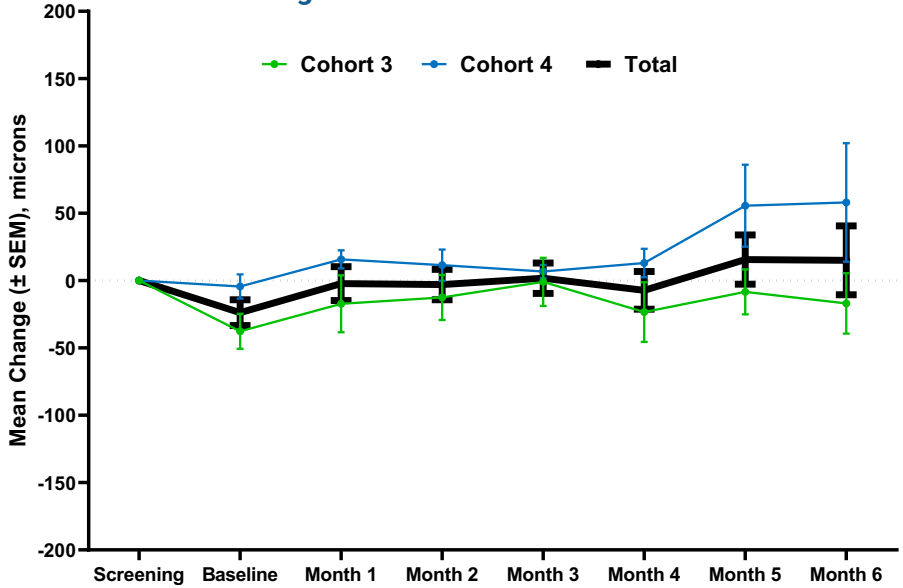
Extension Study (6 Month): Stable Central Subfield Thickness

Mean Central Subfield Thickness, Change from Screening

All Data



Excluding Data After Additional Treatment



Source: Clearside data on file.

OASIS (3 Month) and Extension Study (6 Month) Cohorts 3 and 4: Promising CLS-AX Safety Data, Durability and Biologic Effect

SAFETY DATA

- Excellent safety profile at all doses and timepoints
- No Serious Adverse Events
- No dose limiting toxicities
- No Adverse Events (AEs) from inflammation
- No AEs related to intraocular pressure

DURABILITY

- In OASIS, to 3 months:
  - ≥72% reduction in treatment burden
- In Extension Study, to 6 months:
  - ≥77% reduction in treatment burden
  - Patients not requiring additional therapy:
    - ≥ 3 Months: 11/12 (92%)
    - ≥ 4 Months: 10/12 (83%)
    - **≥ 6 Months: 8/12 (67%)**
    - **> 6 Months: 6/12 (50%)**

BIOLOGIC EFFECT

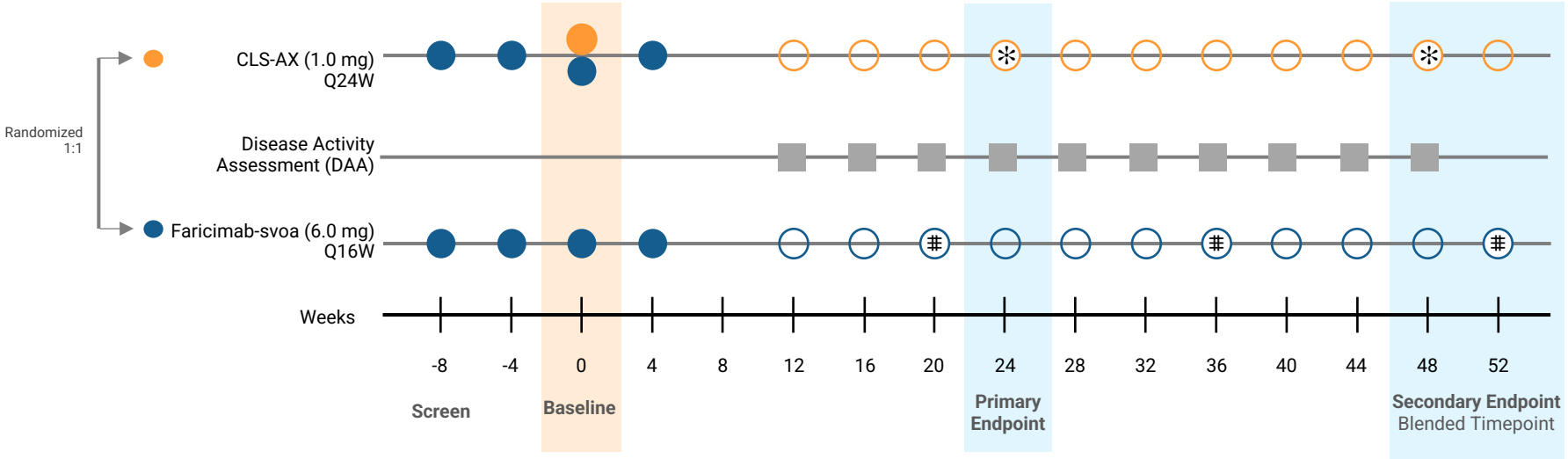
- Stable mean Best Corrected Visual Acuity (BCVA)
- Stable mean Central Subfield Thickness (CST)
- On optical coherence tomography (OCT), anatomical signs of tyrosine kinase inhibitor (TKI) biologic effect were observed in anti-VEGF treatment-experienced sub-responders

NEXT STEPS

- Expect to initiate Phase 2b clinical trial in Q1 2023 with primary endpoint readout anticipated in mid-2024

Source: Clearside data on file.

ODYSSEY Phase 2b Trial Design



•	**Both Arms:**	**4 monthly faricimab loading doses; then monthly disease activity assessments (DAA) with retreatment if required per protocol.**
✻	**CLS-AX Arm:**	**Participants are required to be dosed with CLS-AX at least every 6 months following the last CLS-AX dose. Participants may be dosed sooner than 6 months with CLS-AX if retreatment criteria is met during a DAA.**
#	**Faricimab Arm:**	**Participants are required to be dosed with faricimab at least every 4 months (per label). Participants may be dosed sooner with faricimab if retreatment criteria is met during a DAA. If participants are retreated earlier than 4 months, they will continue to receive further doses of faricimab at that dosing interval for the remainder of the study (per label).**

Note: Proposed clinical trial design.

RGX-314

Phase II AAVIATE Study

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

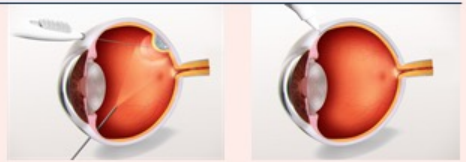
RGX–314 PRODUCT CANDIDATE

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

Route of administration:

Subretinal (nAMD) or

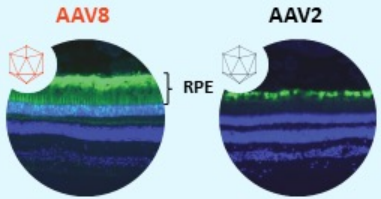
Suprachoroidal (nAMD/DR)



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)**

=

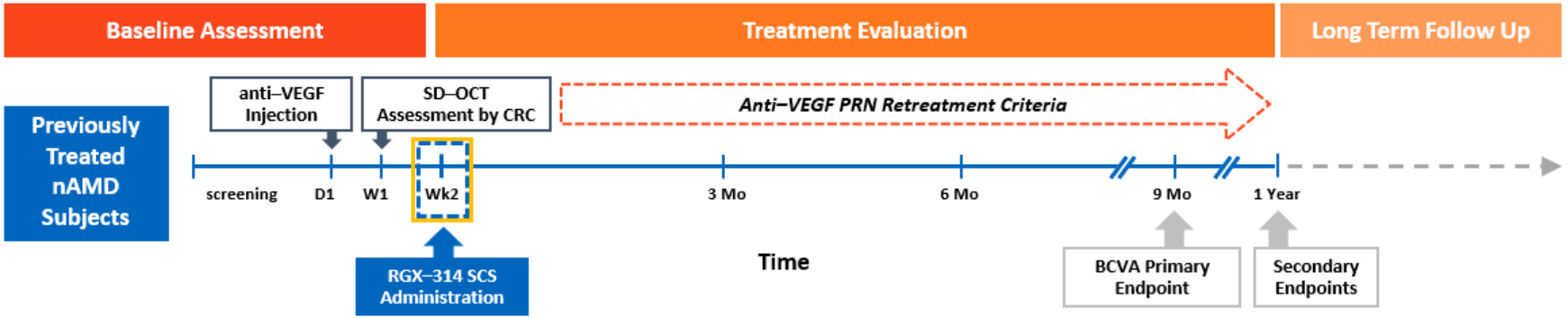
RGX–314: AAV8 encoding anti–VEGF fab

Potential for long-term therapeutic anti-VEGF expression

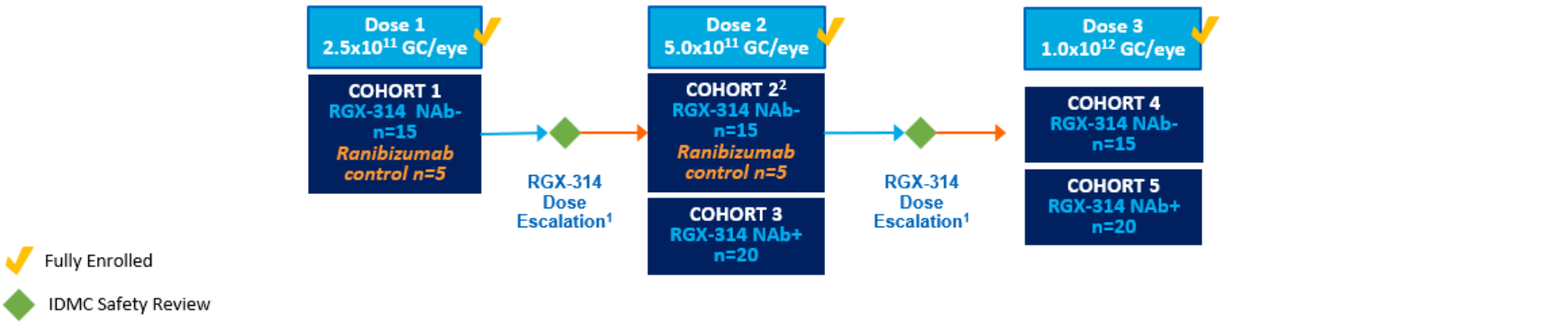
1. Vandenberghe et al. 2011 Science Translational Medicine.

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 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

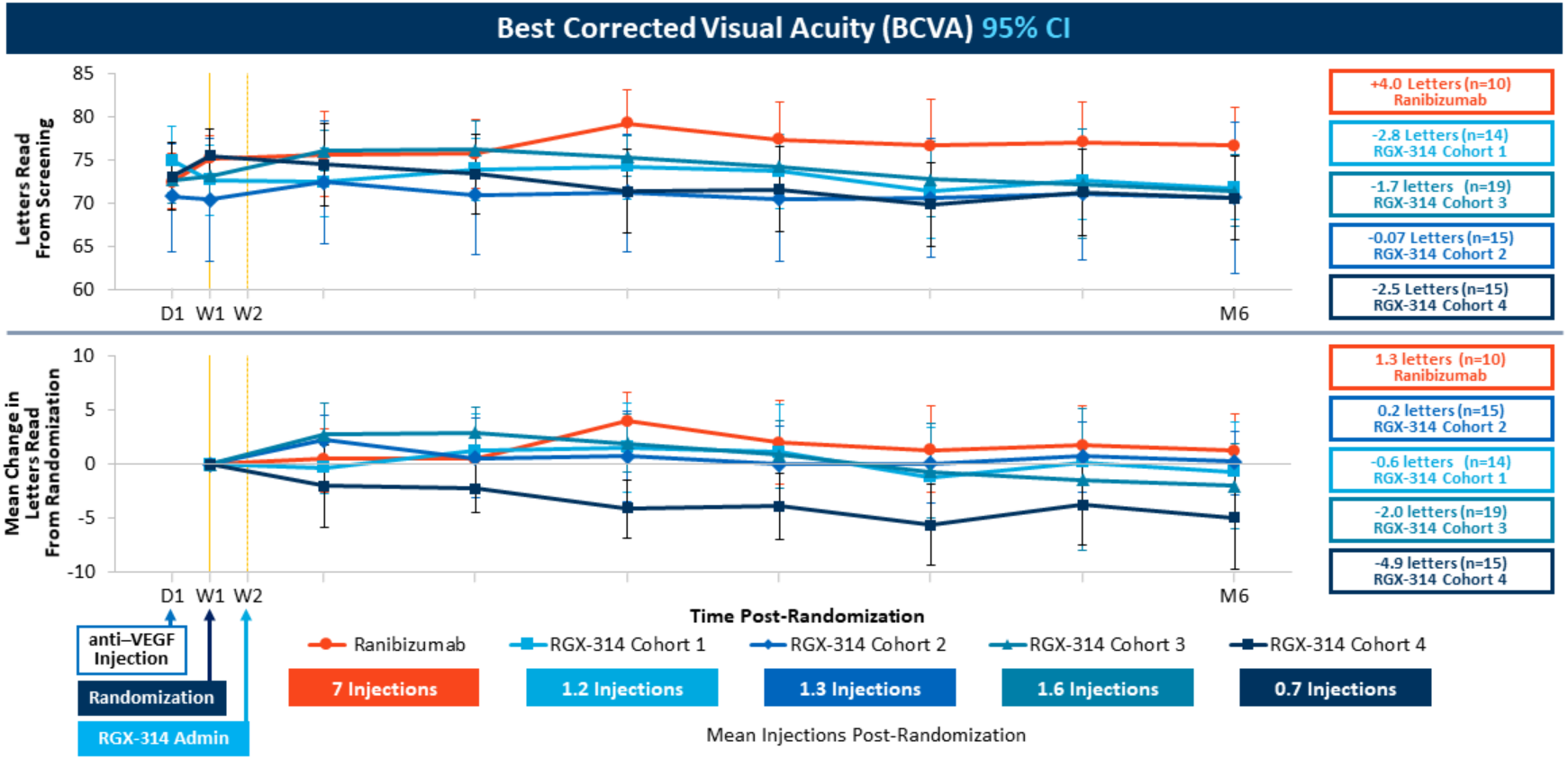
- RGX–314 was well–tolerated in Cohorts 1–5 (n=85) with follow-up ranging from 1–12 months post dosing
  - 15 SAEs: None considered drug-related
  - No cases of chorioretinal vasculitis or occlusion, or hypotony were observed

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**

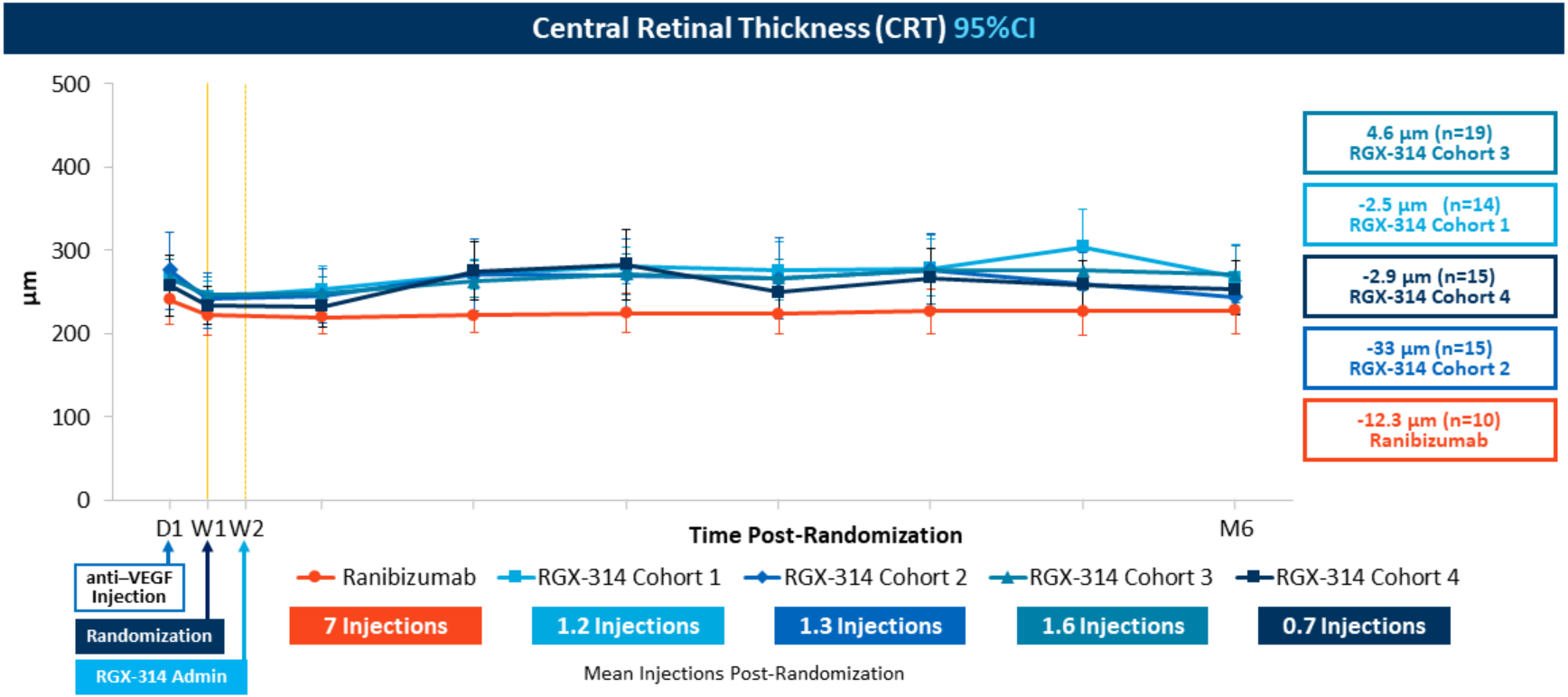
Data cut: August 01, 2022.
1. Includes AEs for total group ≥10% with onset up to 6m visit.
2. All cases were mild to moderate (range +0.5 to 2+), most presented 2-6 weeks post injection, predominantly as anterior cells on slit lamp examination. Resolved on topical corticosteroids.
3. Intraocular pressure 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



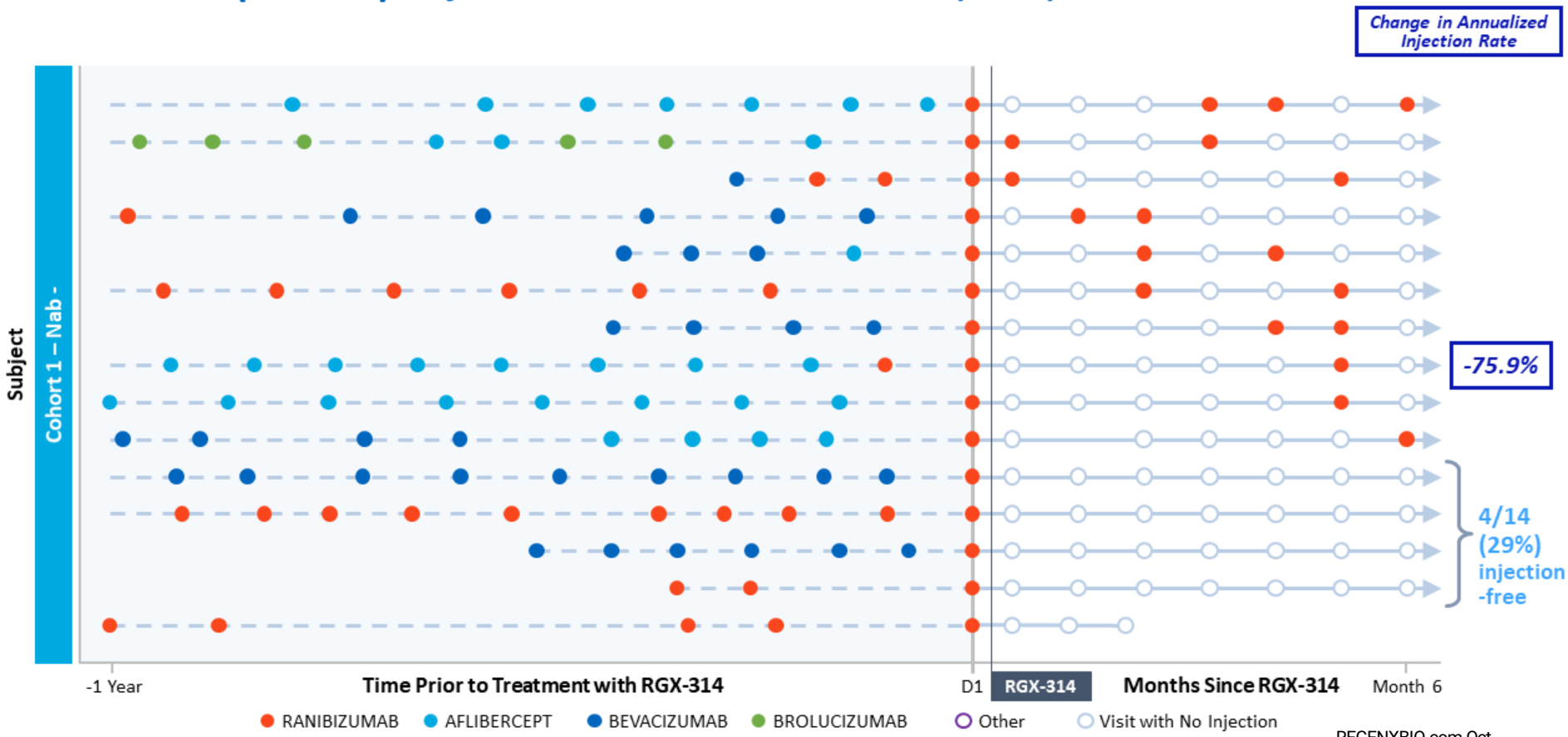
Data cut: August 1, 2022.

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



Data cut: August 1, 2022.

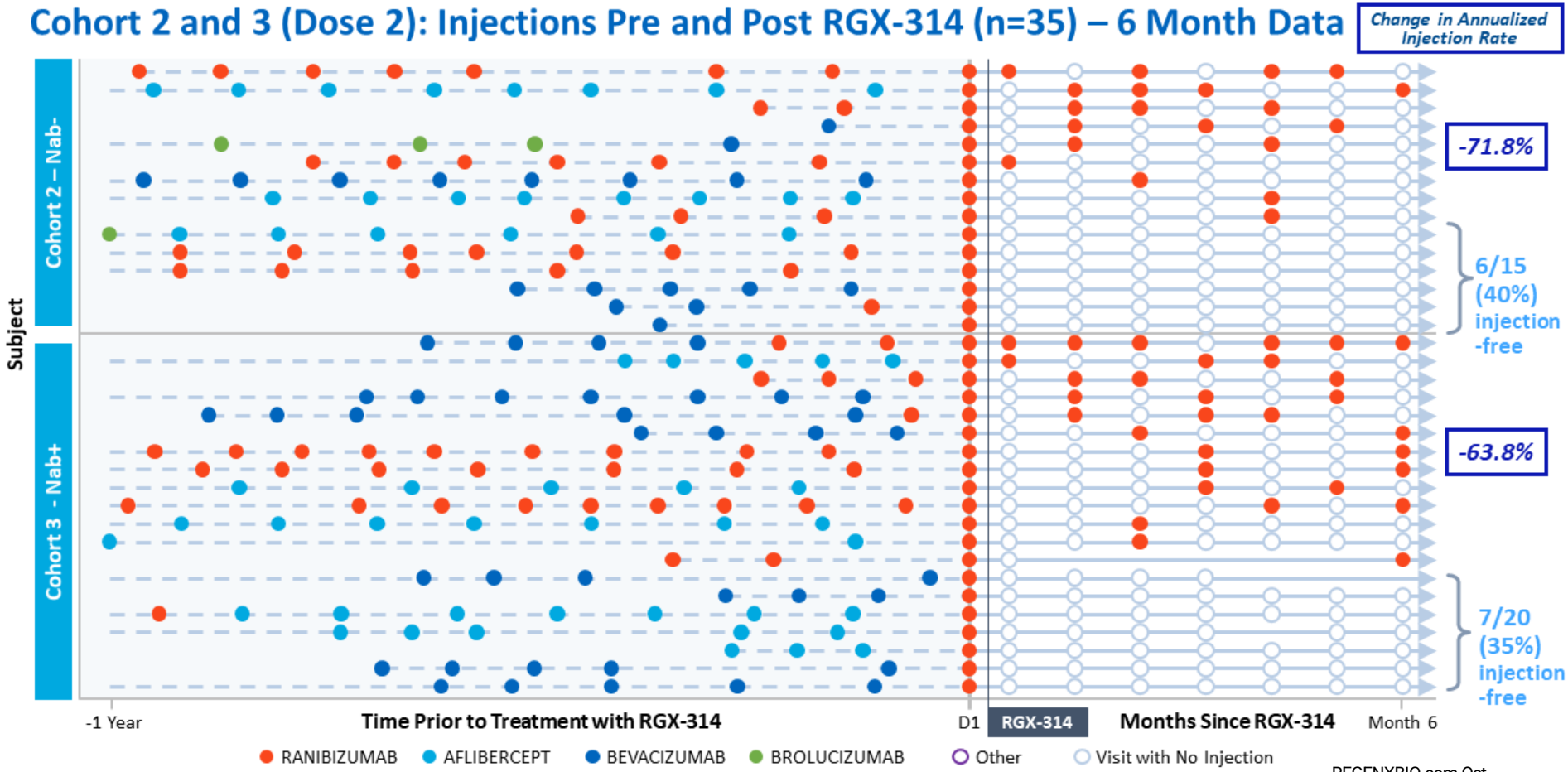
Cohort 1 (Dose 1): Injections Pre and Post RGX-314 (n=15) – 6 Month Data



Data cut: August 1, 2022.

REGENXBIO.com Oct 2022

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



Data cut: August 1, 2022.

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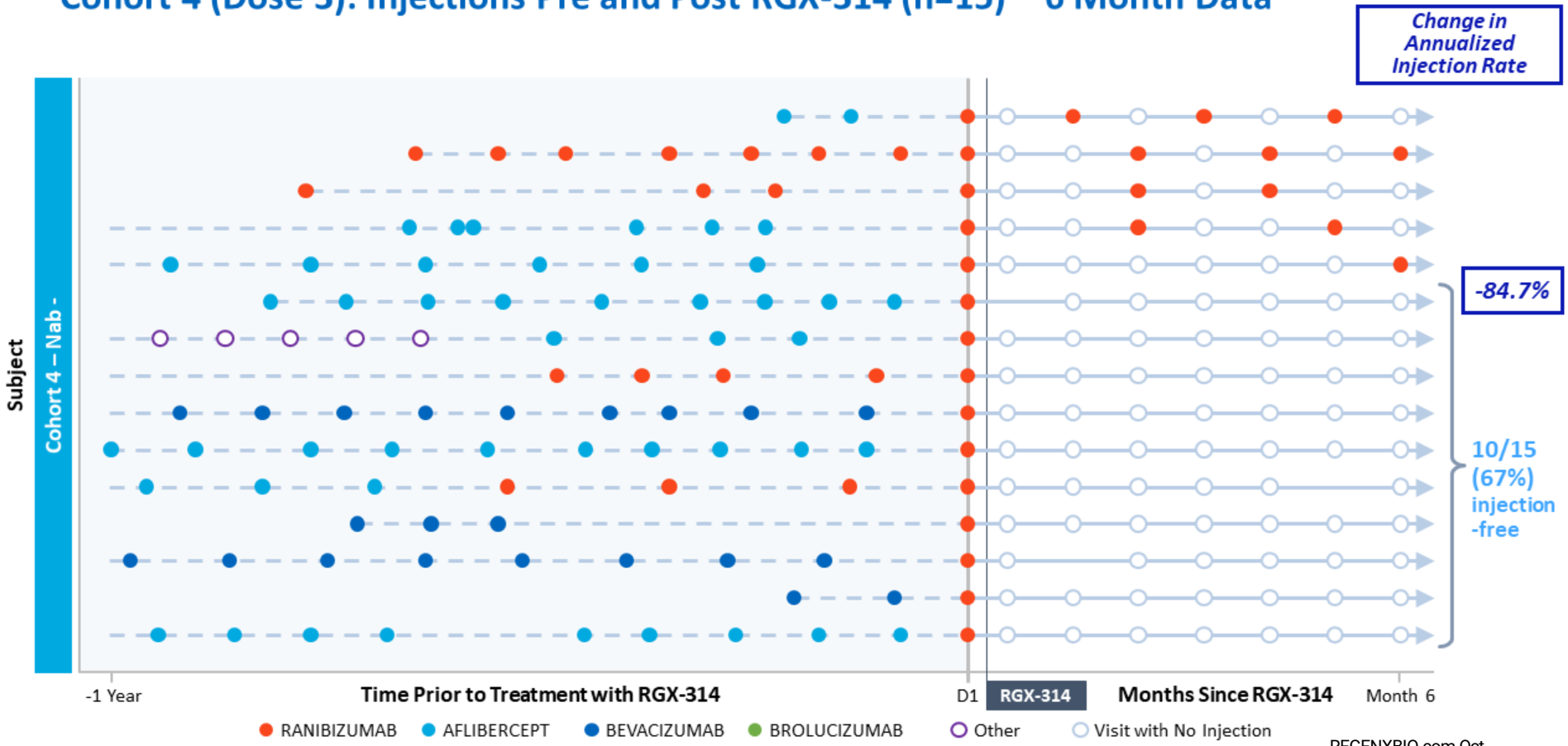
Cohort 4 (Dose 3): Injections Pre and Post RGX-314 (n=15) – 6 Month Data

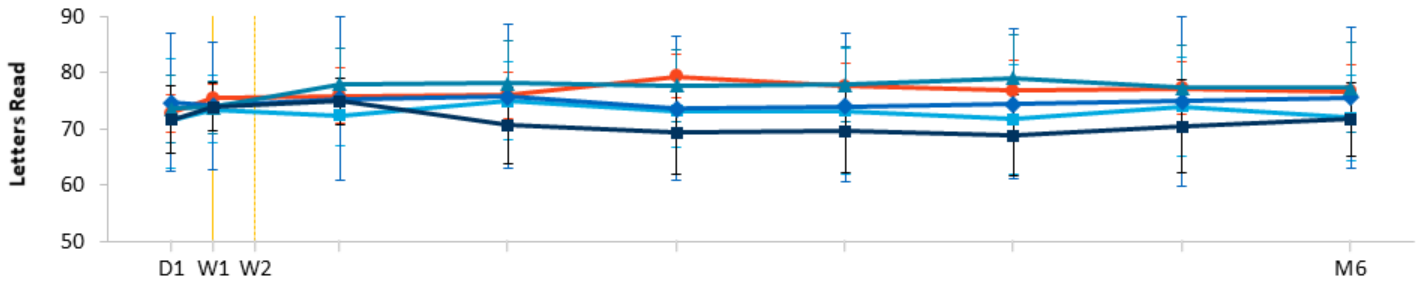


Data cut: August 1, 2022.

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

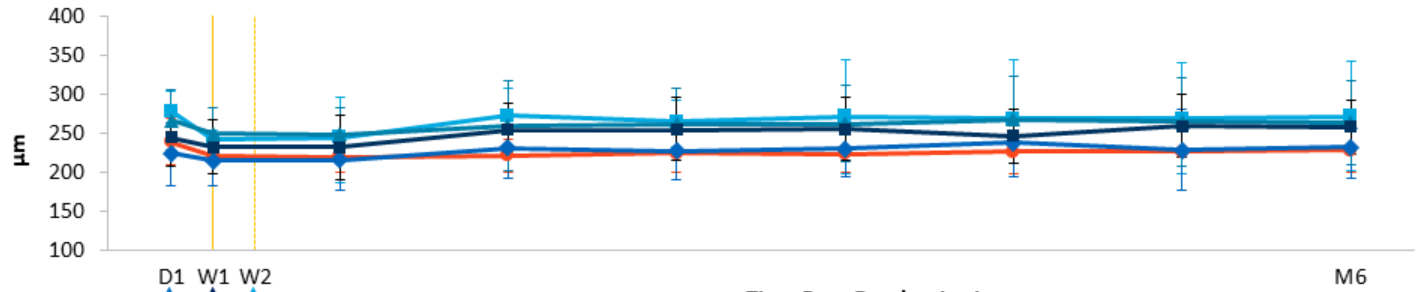
+4.0 Letters (n=10)
Ranibizumab

+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

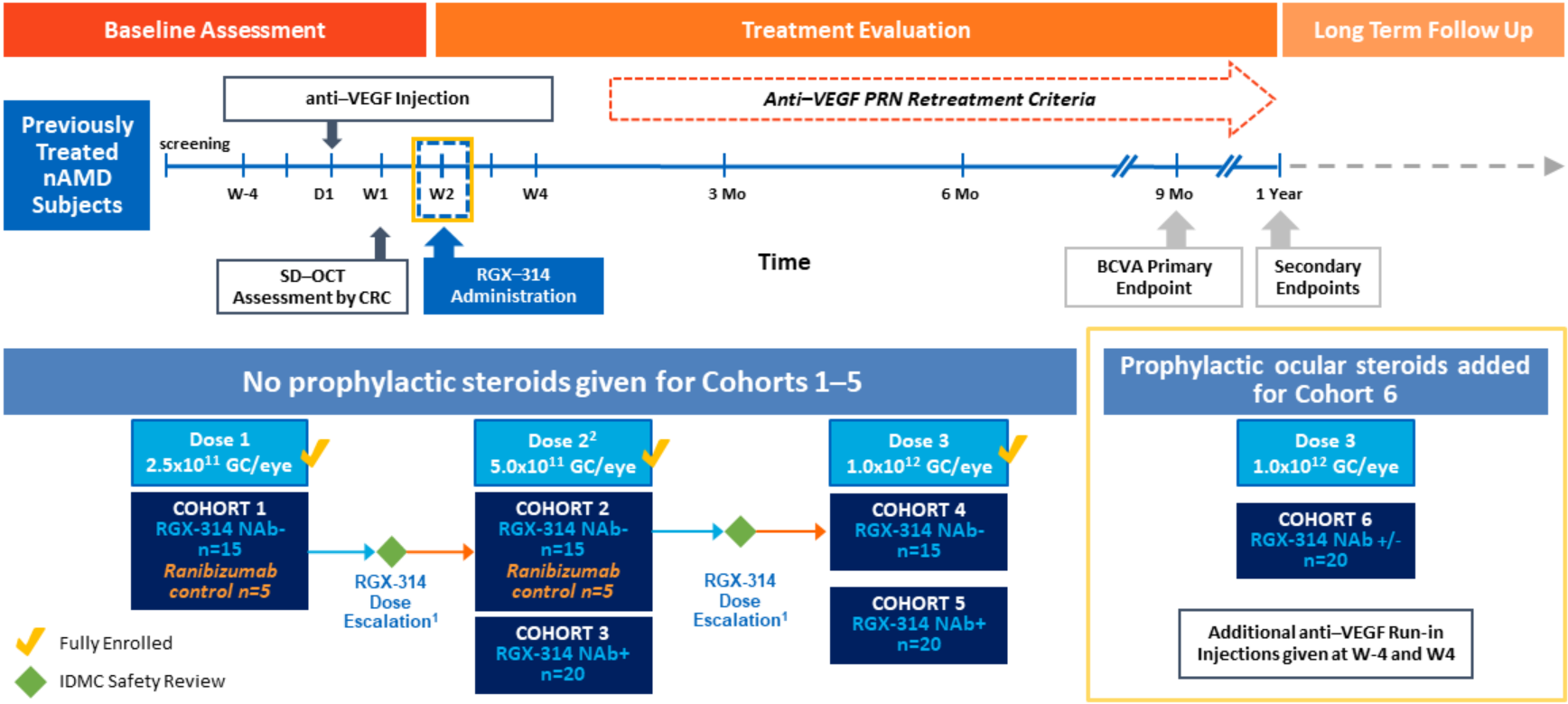
+13.7 µm (n=10)
RGX-314 Cohort 4

+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



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.

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.

Suprachoroidal Therapy for Wet AMD

OASIS RESULTS (CLS-AX):

- **Cohorts 3&4 at 6 Months:**
  - ≥77% Reduction in Treatment Burden
  - 67% No Additional Therapy
- **No SAEs/DLTs**

AAVIATE RESULTS (RGX-314):

- **Cohort 4 at 6 Months:**
  - 85% reduction in treatment burden
  - 67% injection-free
- **Well-tolerated**
  - Mild to Mod IOI resolved w/topical steroids