UT Southwestern
Medical Center

Ophthalmology

Where Are We With Suprachoroidal Delivery?

Judy E. Kim, MD, FARVO, FASRS

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in Honor of James P. McCulley, MD
Professor, Department of Ophthalmology
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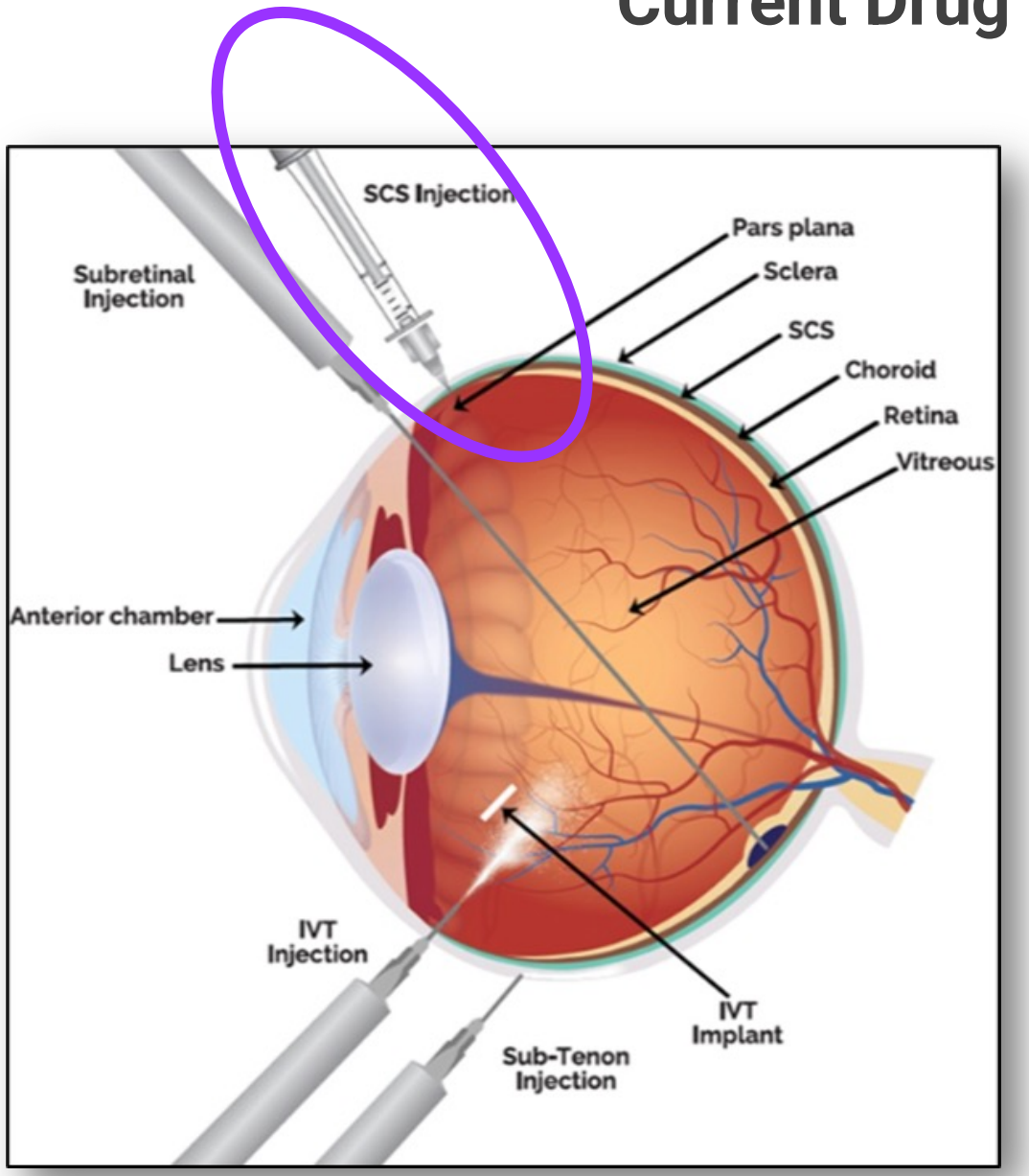
Financial Disclosure

- *Advisory Board/Consultant*:
  - Adverum, Alcon, Alimera, Amgen, Apellis, Bausch + Lomb, Clearside Biomedical, EyePoint, Genentech, Neurotech, Outlook, Regeneron

Current Drug delivery Modalities

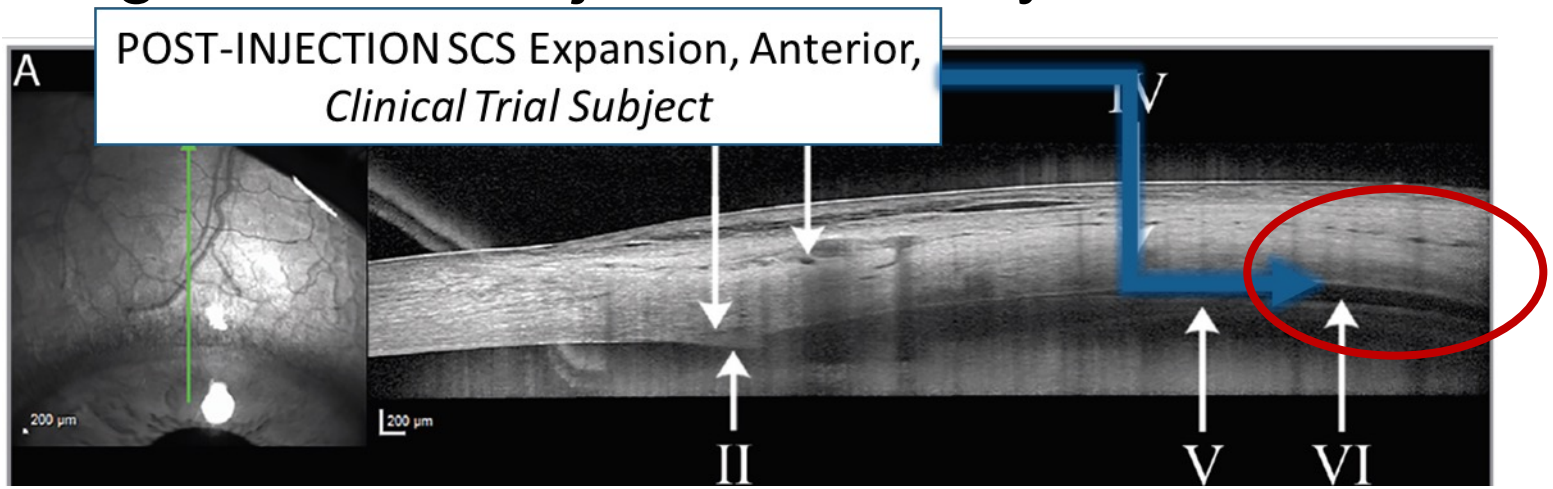


Why suprachoroidal delivery?

Adapted from Ciulla et al. *Am J Manag Care* 2022 and reproduced with permission from Clearside Biomedical, Inc.

Suprachoroidal Drug Delivery

- Suprachoroidal space (SCS) is a potential space which expands with the introduction of fluid
- Injection into the SCS presents an opportunity for targeted delivery of high levels of injectate directly to affected chorioretinal tissues



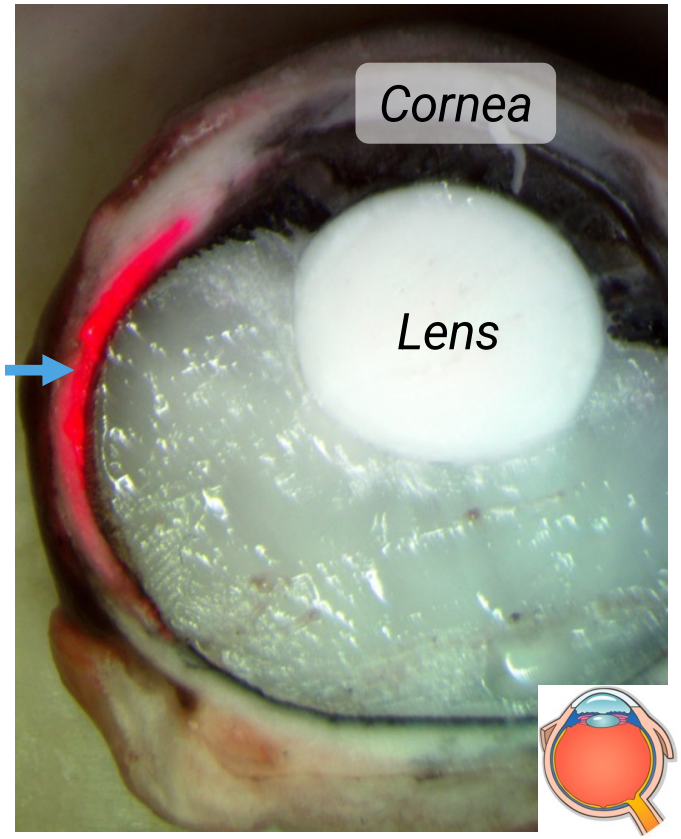
TARGETED
for efficacy

COMPARTMENTALIZED
for safety

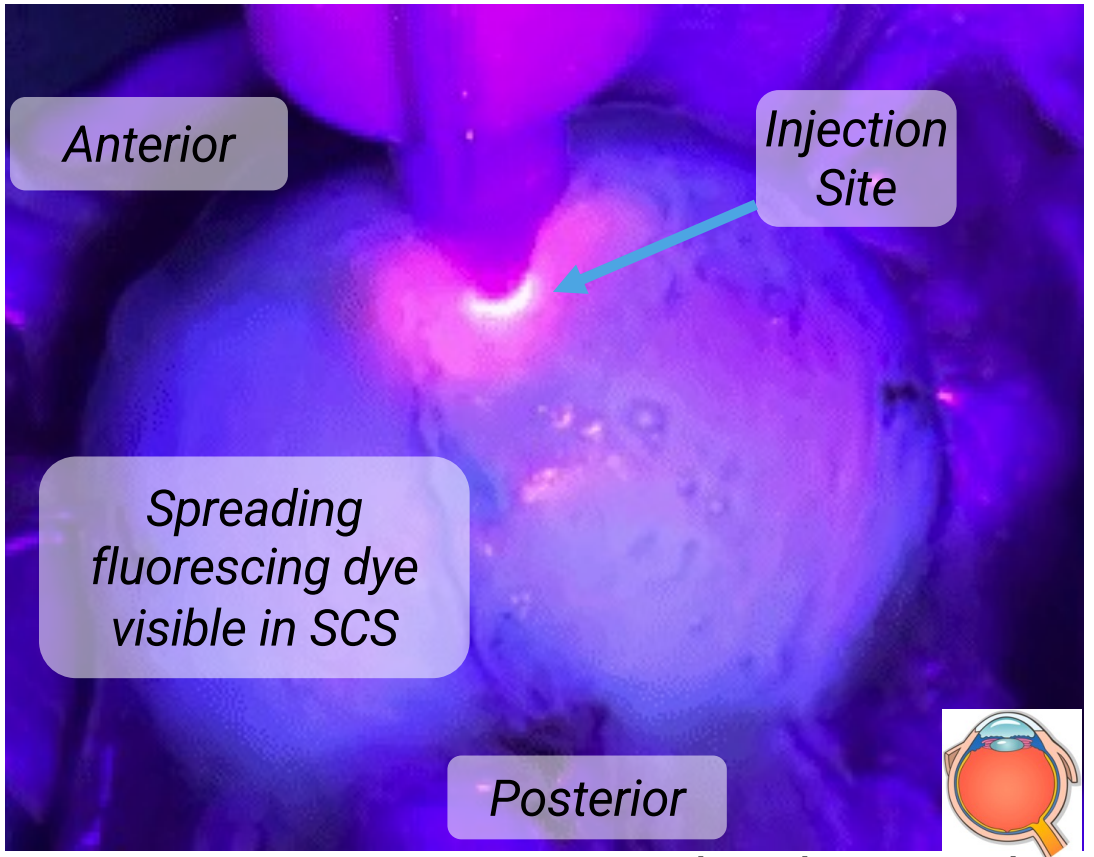
BIOAVAILABLE & PROLONGED DRUG LEVELS
for durability

SCS injection of dye shows posterior circumferential spread around the globe[1]

Ex Vivo Porcine Model



Cross-section: *Injectate spreads from scleral spur towards macula*



Top View: *Injectate immediately spreads from injection site to posterior tissues*

Sources: Clearside data on file | 1. Marcus, et. al, Retina Society 2021 *Comparison of Suprachoroidal and Intravitreal Injection Flow Mechanics Analyzed via Multimodal Imaging*

IOP > Anterior SCS Pressure > Posterior SCS Pressure
A Driving Force for Uveoscleral Outflow

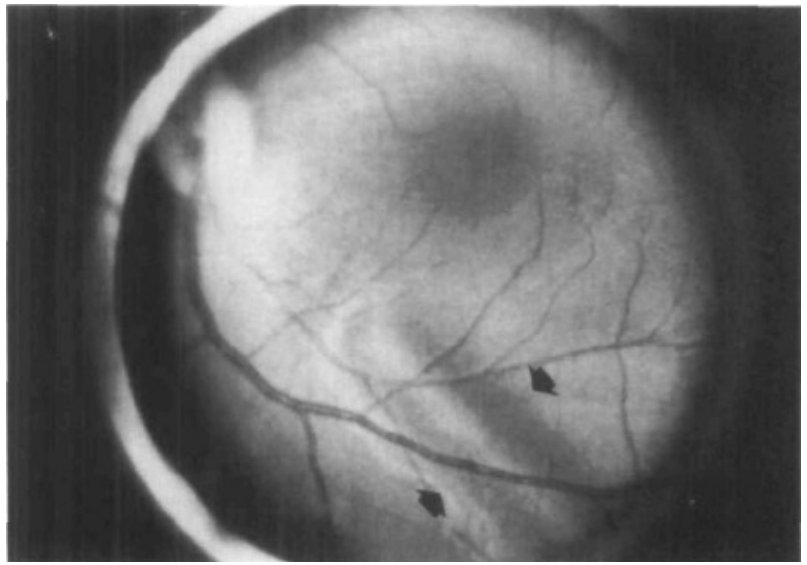
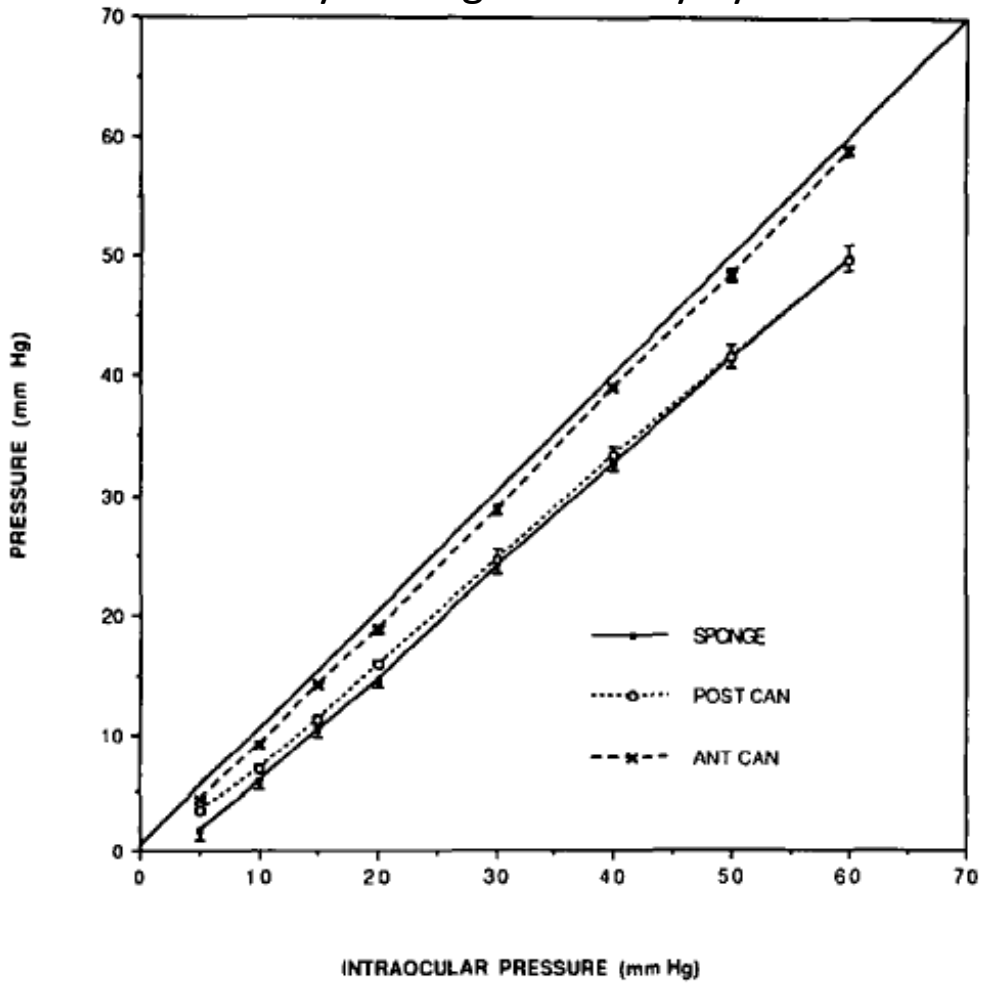


Table 1. Spontaneous pressure measurements (mm Hg)

	Anterior cannula	*Posterior cannula*	*Sponge*
IOP	9.4 ± 0.9 (9)*	9.2 ± 0.9 (10)†	9.3 ± 1.2 (7)‡
SCSP	8.4 ± 0.9 (9)*	5.8 ± 0.5 (10)†	5.1 ± 1.2 (7)‡
IOP-SCSP	0.9 ± 0.2 (9)§‖	3.5 ± 0.5 (10)§	4.2 ± 0.5 (7)‖

Each value indicates mean ± SE. ( ) = n. IOP: intraocular pressure. SCSP: suprachoroidal space pressure. *$P < 0.05$, †‡$P < 0.001$ (paired student t-test). §‖$P < 0.001$ (unpaired student t-test).

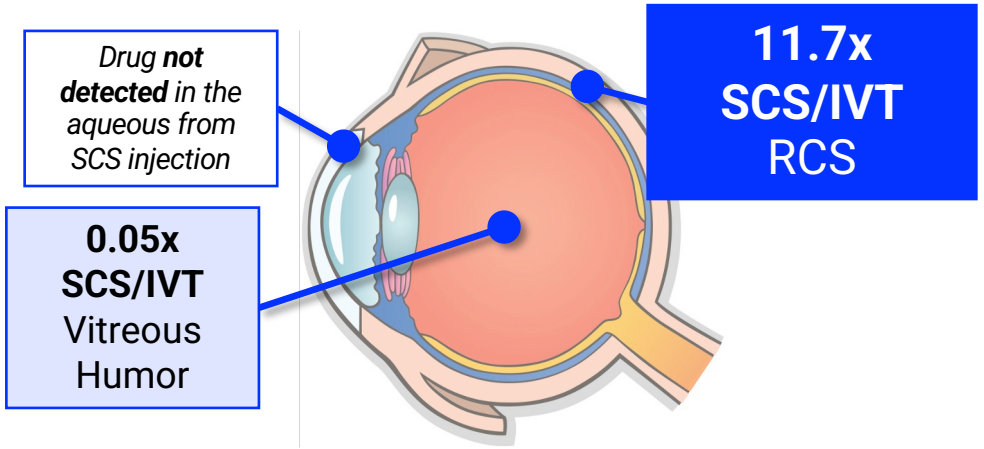
18 cynomolgus monkey eyes



Emi K, Pederson JE, Toris CB. Hydrostatic pressure of the suprachoroidal space. *Invest Ophthalmol Vis Sci*. 1989;30(2):233-238.

For small molecule suspensions, preclinical testing shows 11X greater levels in posterior tissues when delivered to SCS vs IVT at equivalent doses

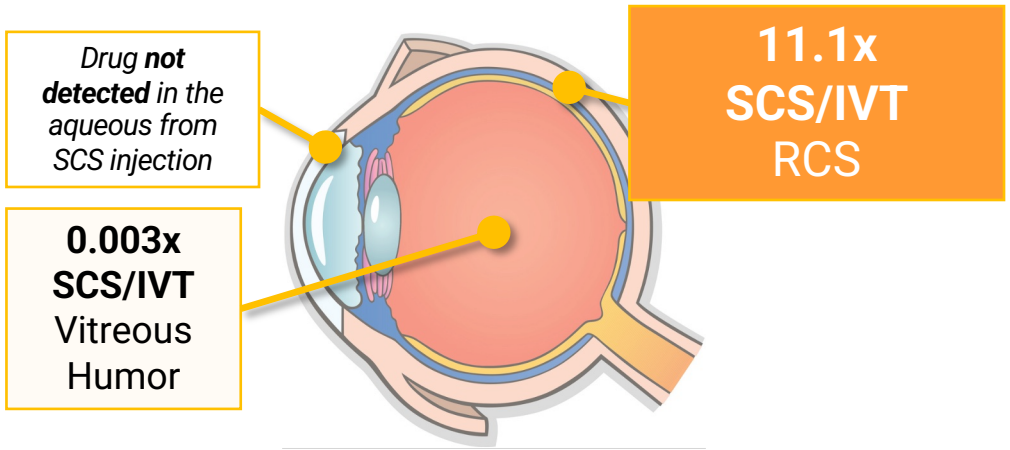
SCS / IVT Ratios for injected triamcinolone acetonide, by tissue type *(4 mg / eye)*



Values are area under the curve ratios (SCS / IVT) over 91 days in rabbit eyes

Triamcinolone acetonide injectable suspension for suprachoroidal use is FDA approved for the treatment of uveitic macular edema

SCS / IVT Ratios for injected axitinib, by tissue type *(1 mg / eye)*



Values are area under the curve ratios (SCS / IVT) over 7 days in rabbit eyes

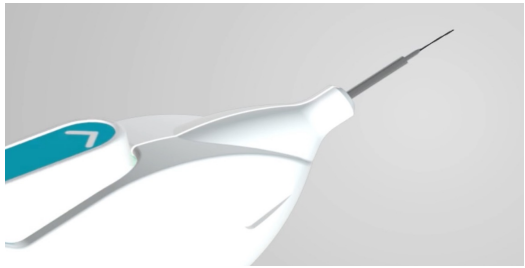
Axitinib injectable suspension for suprachoroidal use (CLS-AX) is currently under evaluation in clinical trials.

Leroy Muya, Viral Kansara, Megan E. Cavet, and Thomas Ciulla.Suprachoroidal Injection of Triamcinolone Acetonide Suspension: Ocular Pharmacokinetics and Distribution in Rabbits Demonstrates High and Durable Levels in the Chorioretina.Journal of Ocular Pharmacology and Therapeutics.ahead of printhttp://doi.org/10.1089/jop.2021.0090

Viral S. Kansara, Leroy W. Muya, Thomas A. Ciulla; Evaluation of Long-Lasting Potential of Suprachoroidal Axitinib Suspension Via Ocular and Systemic Disposition in Rabbits. *Trans. Vis. Sci. Tech.* 2021;10(7):19. doi: https://doi.org/10.1167/tvst.10.7.19.

Different Programs Developing Suprachoroidal Delivery Methods

FDA approved and commercially available for SCS injection of triamcinolone acetonide for uveitic macular edema



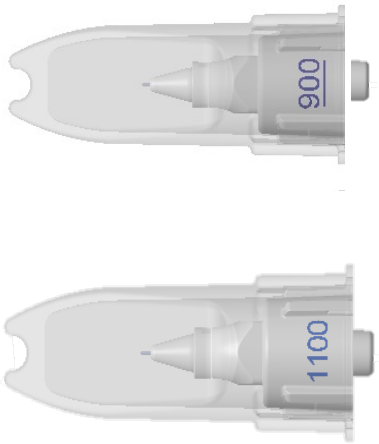
Suprachoroidal delivery methods include microneedle injection and microcatheterization

SCS Injection with the SCS Microinjector®

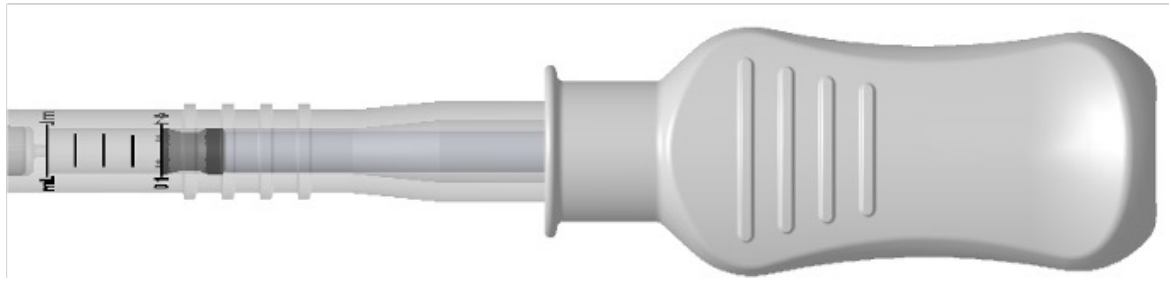
- Two 30-gauge needles of two lengths included to accommodate variation in patient anatomy

900 µm and 1100 µm Needles

shown capped



SCS Microinjector® Syringe



Injection Technique

RETINA
THE JOURNAL OF RETINAL AND VITREOUS DISEASES

REVIEW

SUPRACHOROIDAL SPACE INJECTION TECHNIQUE

Expert Panel Guidance

Wykoff, Charles C. MD, PhD[*]; Avery, Robert L. MD[†]; Barakat, Mark R. MD[‡,§]; Boyer, David S. MD[¶]; Brown, David M. MD[*]; Brucker, Alexander J. MD[**]; Cunningham, Emmett T. Jr MD, PhD, MPH[††,‡‡,§§,¶¶]; Heier, Jeffrey S. MD[***]; Holekamp, Nancy M. MD[†††,‡‡‡]; Kaiser, Peter K. MD[§§§]; Khanani, Arshad M. MD, MA[¶¶¶,****]; Kim, Judy E. MD[††††]; Demirci, Hakan MD[‡‡‡‡]; Regillo, Carl D. MD[§§§§]; Yiu, Glenn C. MD, PhD[¶¶¶¶]; Ciulla, Thomas A. MD, MBA[*****]

Retina. 2024 Jun 1;44(6):939-949.

RETINA
SPECIALIST

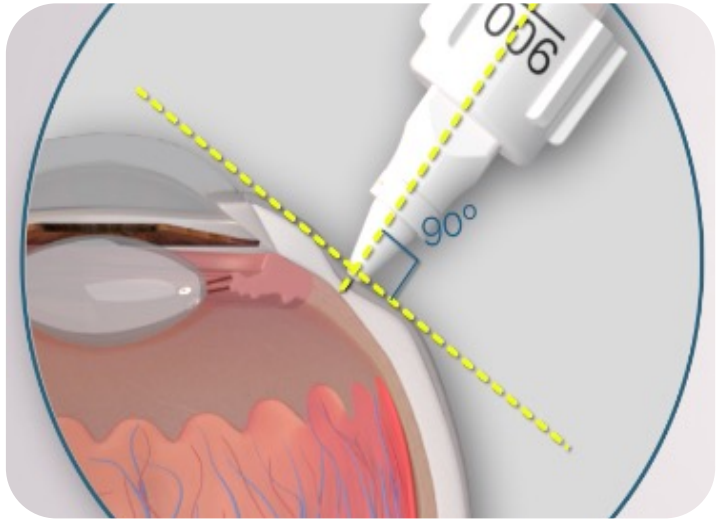
A beginner's guide to suprachoroidal injections

They require a different skill set than intravitreal injections. Here's a description of the technique.

By Carol Villafuerte-Trisolini, MD, and Glenn Yiu, MD, PhD

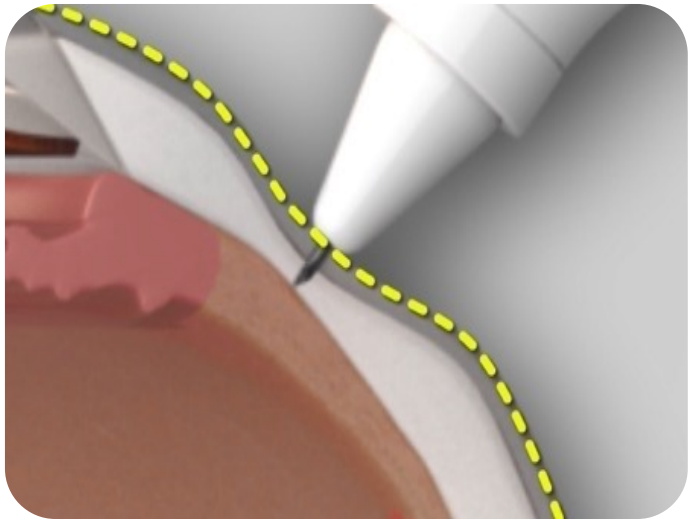
DECEMBER 23, 2023

Suprachoroidal Injection Technique Using the SCS Microinjector®



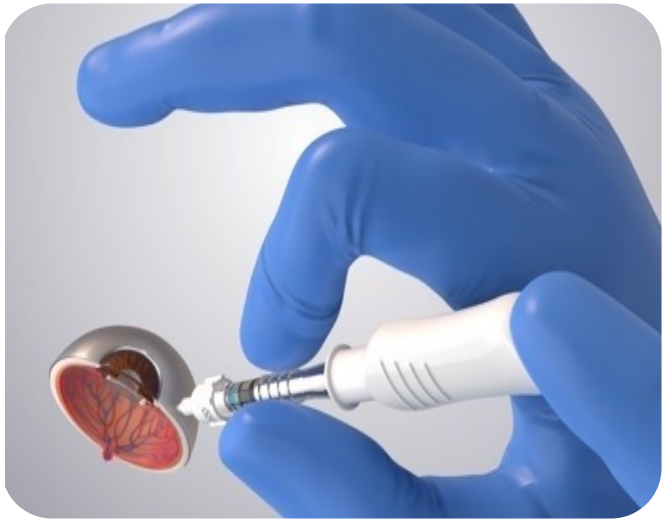
Perpendicular

Hold the microinjector **perpendicular** to the ocular surface



Dimple

Ensure firm contact with sclera by maintaining a **dimple** throughout injection



Slow

Inject **slowly** over 5 – 10 seconds

Source: Clearside July 24, 2024 KOL Webinar

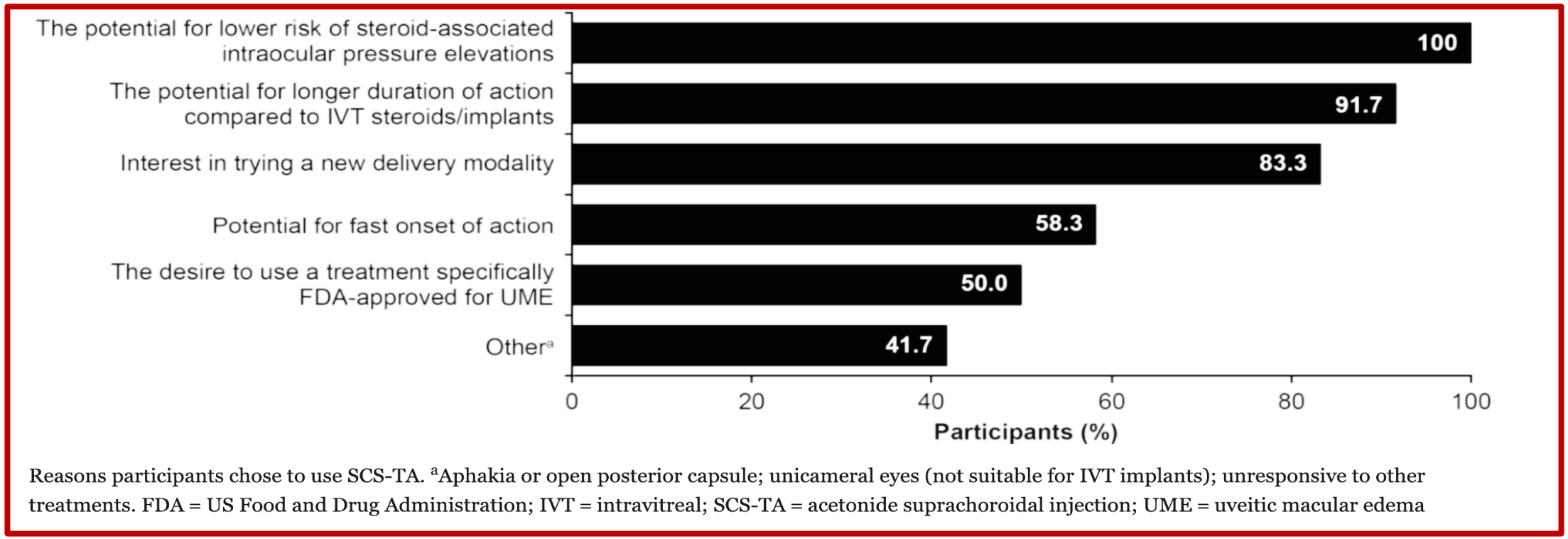
Response from Physicians Using Suprachoroidal Therapy

- "Nearly all participants (92%) found the injection procedure relatively easy post-training, with most (75%) procedurally comfortable after completing 2-5 injections."
- "… **this treatment has potential applications for patients with other ophthalmic conditions**…" besides uveitic macular edema.

BMC Part of Springer Nature

Early adoption of triamcinolone acetonide suprachoroidal injection for uveitic macular edema: a physician survey

Henry, C.R., et al. BMC Res Notes 17, 317 (2024)

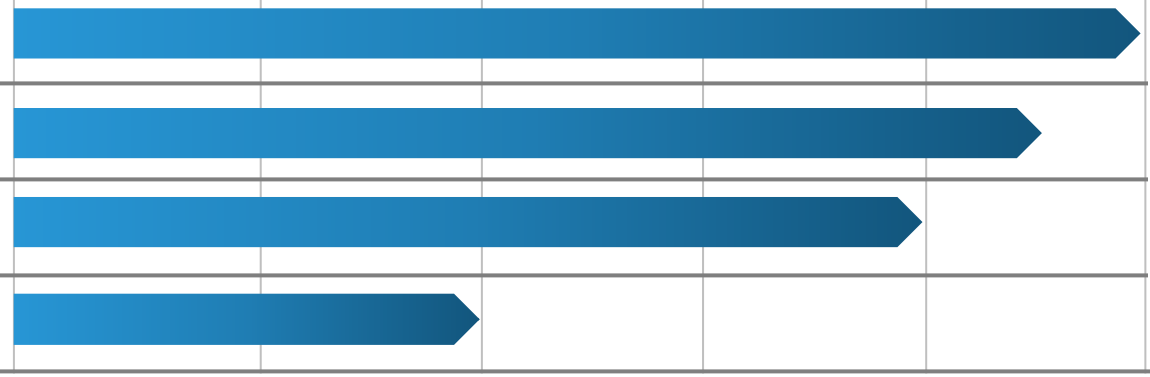


Reasons participants chose to use SCS-TA. [a]Aphakia or open posterior capsule; unicameral eyes (not suitable for IVT implants); unresponsive to other treatments. FDA = US Food and Drug Administration; IVT = intravitreal; SCS-TA = acetonide suprachoroidal injection; UME = uveitic macular edema

Studies Underway Using the SCS Microinjector

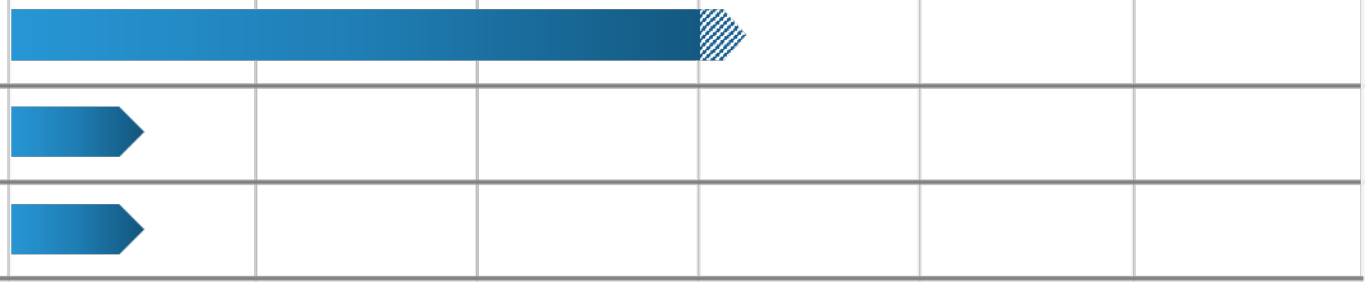
Triamcinolone acetonide injectable suspension for suprachoroidal use

LOCATION	INDICATION	PRE-CLINICAL	PHASE 1	PHASE 2	PHASE 3	APPROVAL
United States	Uveitic Macular Edema[1]					
Australia Singapore	Uveitic Macular Edema[2]					
China	Uveitic Macular Edema[2]					
Asia Pacific ex-Japan	Diabetic Macular Edema[2]					



Research and Clinical Development Programs

THERAPEUTIC	MECHANISM	INDICATION	PRE-CLINICAL	PHASE 1	PHASE 2	PHASE 3	APPROVAL	COMPANY
CLS-AX (axitinib)	Tyrosine Kinase Inhibitor	Wet AMD						
Undisclosed	Improve choroidal perfusion	Geographic Atrophy (GA)						
Undisclosed	Modulate pro-inflammatory cells	Geographic Atrophy (GA)						



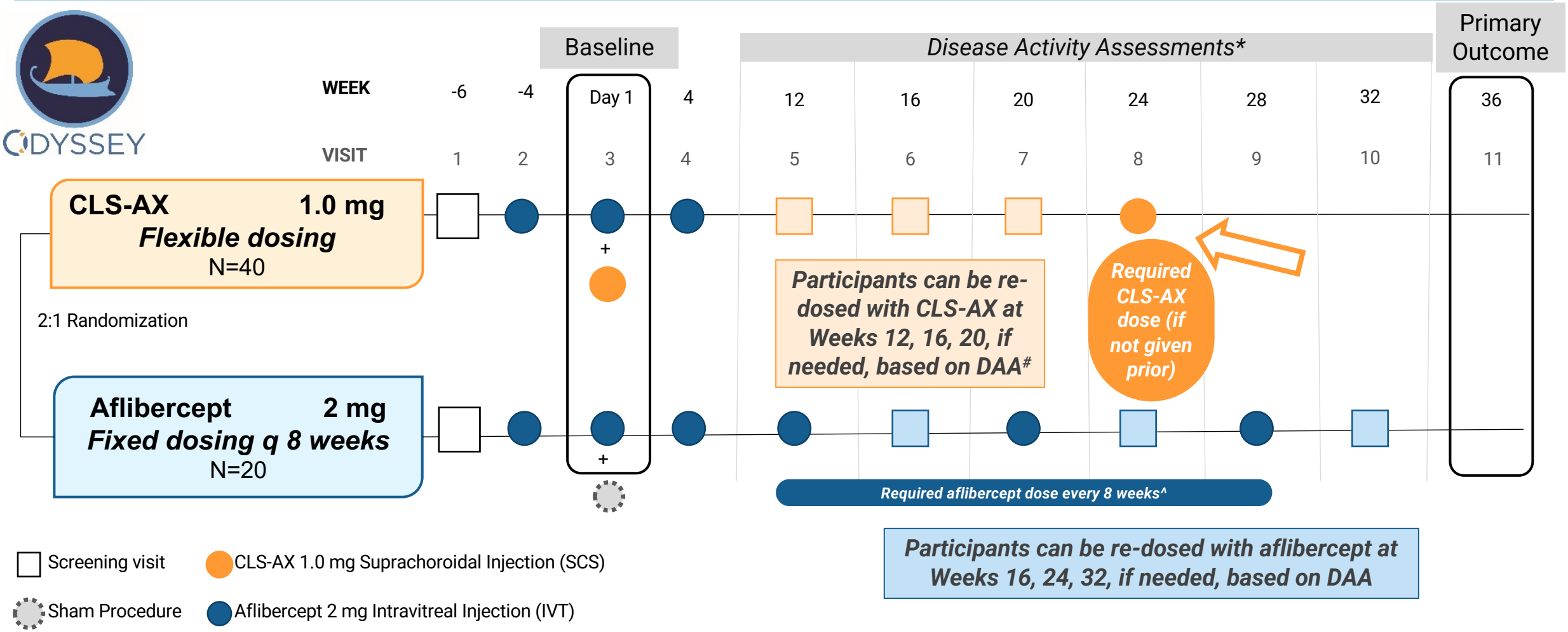
Suprachoroidal CLS-AX
Phase 2b Topline Data Results in Wet AMD

- Axitinib: a tyrosine kinase inhibitor (TKI) approved to treat renal cell cancer
- Achieves pan-VEGF blockade, inhibiting VEGF receptors-1, -2, and -3
- Broad VEGF blockade may have efficacy advantages over existing retinal therapies by acting at a different level of the angiogenesis cascade
- May benefit patients who sub-optimally respond to current, more narrowly focused anti-VEGF therapies

Preliminary Topline Results
Subject to Change

ODYSSEY Trial for nAMD Design: Axitinib

TKI with pan-VEGF inhibition



#Participants can be re-dosed with CLS-AX up to every 12 weeks; All arms are sham controlled

* Disease Activity Assessments (DAA): Conducted at Week 12 through 32 to determine need for supplemental treatment.
# In CLS-AX arm, following 3 loading doses of aflibercept and initial dose of CLS-AX at Baseline, participants will receive CLS-AX at least every 24 weeks unless more frequently required based on DAA;
if disease is active and participant is <12 weeks since last CLS-AX injection, participant receives dose of aflibercept;
if disease is active and participant is >12 weeks since last CLS-AX injection, participant receives dose of CLS-AX.
^ In aflibercept arm, following 3 loading doses of aflibercept, participants will receive aflibercept on fixed dosing regimen every 8 weeks unless more frequently required based on DAA;
if disease is active, participant receives dose of aflibercept.

ODYSSEY Data Support CLS-AX Progressing to Phase 3

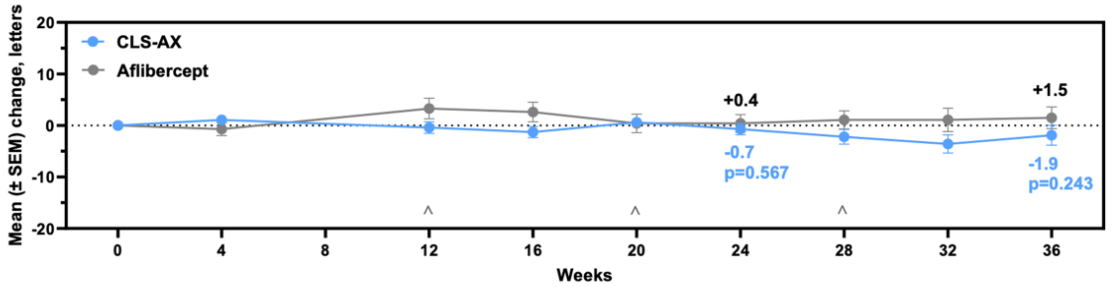
- **Achieved Primary Objective: Stable BCVA to Week 36 in difficult-to-treat nAMD participants with confirmed activity**

Stable Best Corrected Visual Acuity (BCVA) and Central Subfield Retinal Thickness (CST) Over 36 Weeks

CLS-AX results do not include supplemental therapy with aflibercept

BCVA

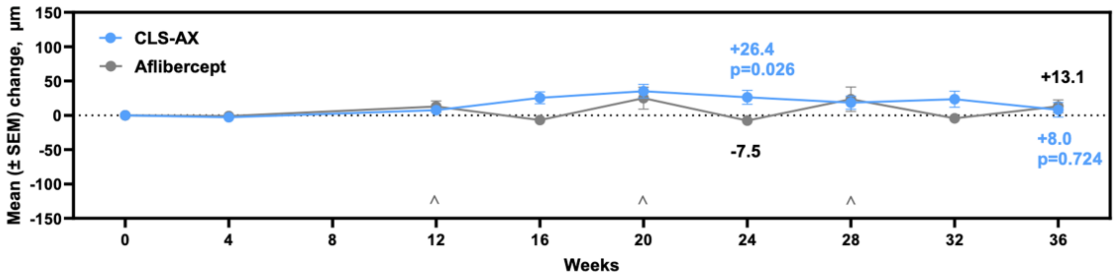
Within 2 letters from Baseline at Week 24 and Week 36 in CLS-AX arm



CST

Stable anatomical control

Reduces fluctuation



^Study drug administration for aflibercept participants given at Weeks 12, 20 and 28.
Abbreviations: BCVA = best corrected visual acuity; CST = central subfield thickness – as reported by the reading center
SEM = standard error of the mean.
P-value based on a 2-sample t-test between treatment groups .

Preliminary Topline Results Subject to Change

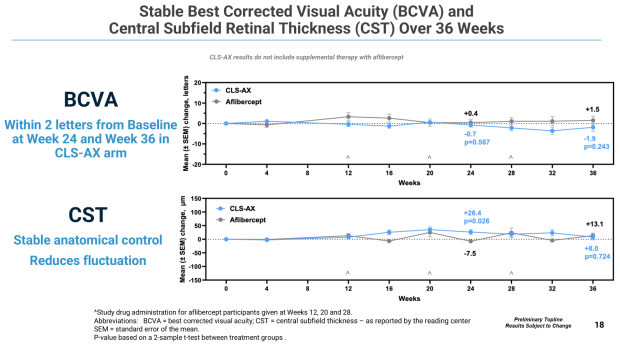
18

Calculation accounts for missed treatments; time of initial administration of study drug shown as month 0 on figure.
Intervention-free rate calculation: if participant received intervention at a study visit, those were reflected in the count at the following study visit.

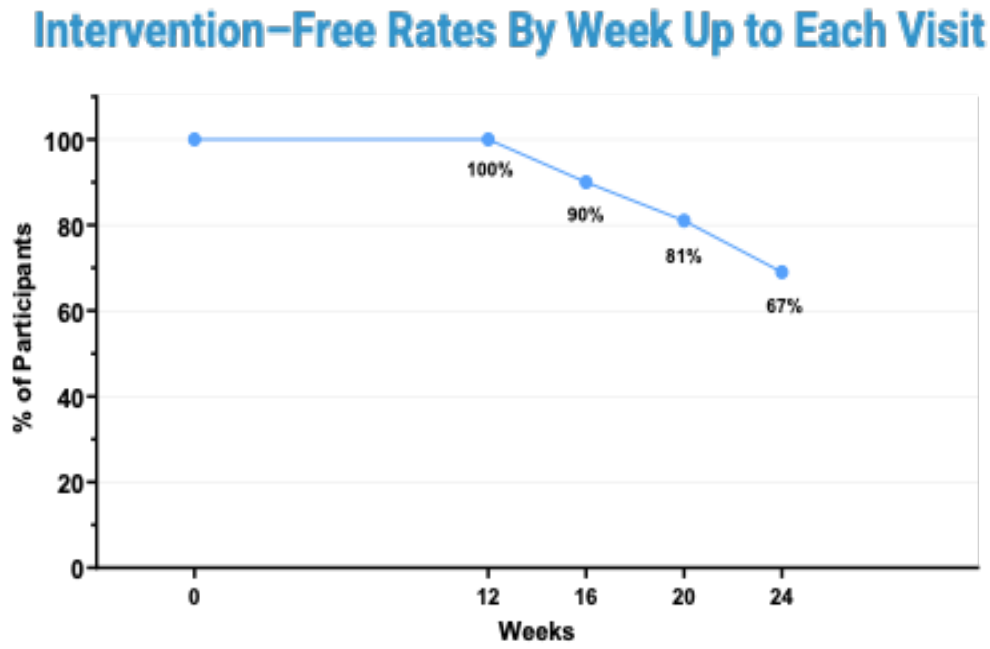
Preliminary Topline Results Subject to Change

ODYSSEY Data Support CLS-AX Progressing to Phase 3

- **Achieved Primary Objective: <u>Stable</u> BCVA to Week 36 in difficult-to-treat nAMD participants with confirmed activity**



- **67% injection free at 6 months**
- **Injection frequency over all reduced by nearly 84%**



Calculation accounts for missed treatments; time of initial administration of study drug shown as month 0 on figure. Intervention-free rate calculation: if participant received intervention at a study visit, those were reflected in the count at the following study visit.

Preliminary Topline Results Subject to Change

CLS-AX Demonstrated Positive Safety Profile

No Ocular SAEs and No Treatment-Related SAEs

- No drug or procedure-related ocular SAEs
- No reported drug or procedure-related systemic SAEs
- No endophthalmitis
- No retinal vasculitis

Only Phase 2 trial in wet AMD with repeat TKI dosing data to potentially de-risk Phase 3 design

Two pivotal, non-inferiority Phase 3 trials being planned to start 2H 2025

Two arms with ~225 participants per arm: CLS-AX 1 mg vs aflibercept 2 mg

Abbreviations: AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Preliminary Topline Results Subject to Change

Suprachoroidal Gene Therapy with ABBV-RGX-314 for Neovascular AMD: The Phase 2 AAVIATE® Study

V:16Jan24

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

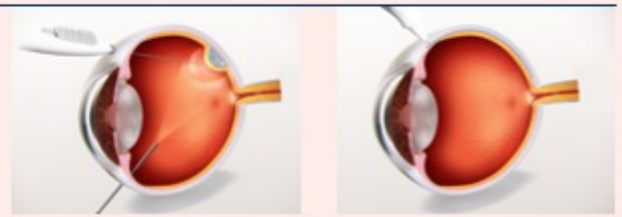
ABBV-RGX–314 PRODUCT CANDIDATE

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

Route of administration:

Subretinal (nAMD) or

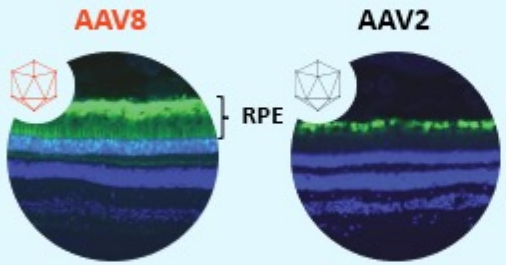
Suprachoroidal (nAMD/DR)



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

=

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

Primary Objective

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

Secondary Objectives

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

Retreatment Criteria

- Based on worsening vision and/or fluid

Subjects: 116 patients enrolled in Dose Levels 1-3

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

Route of Administration

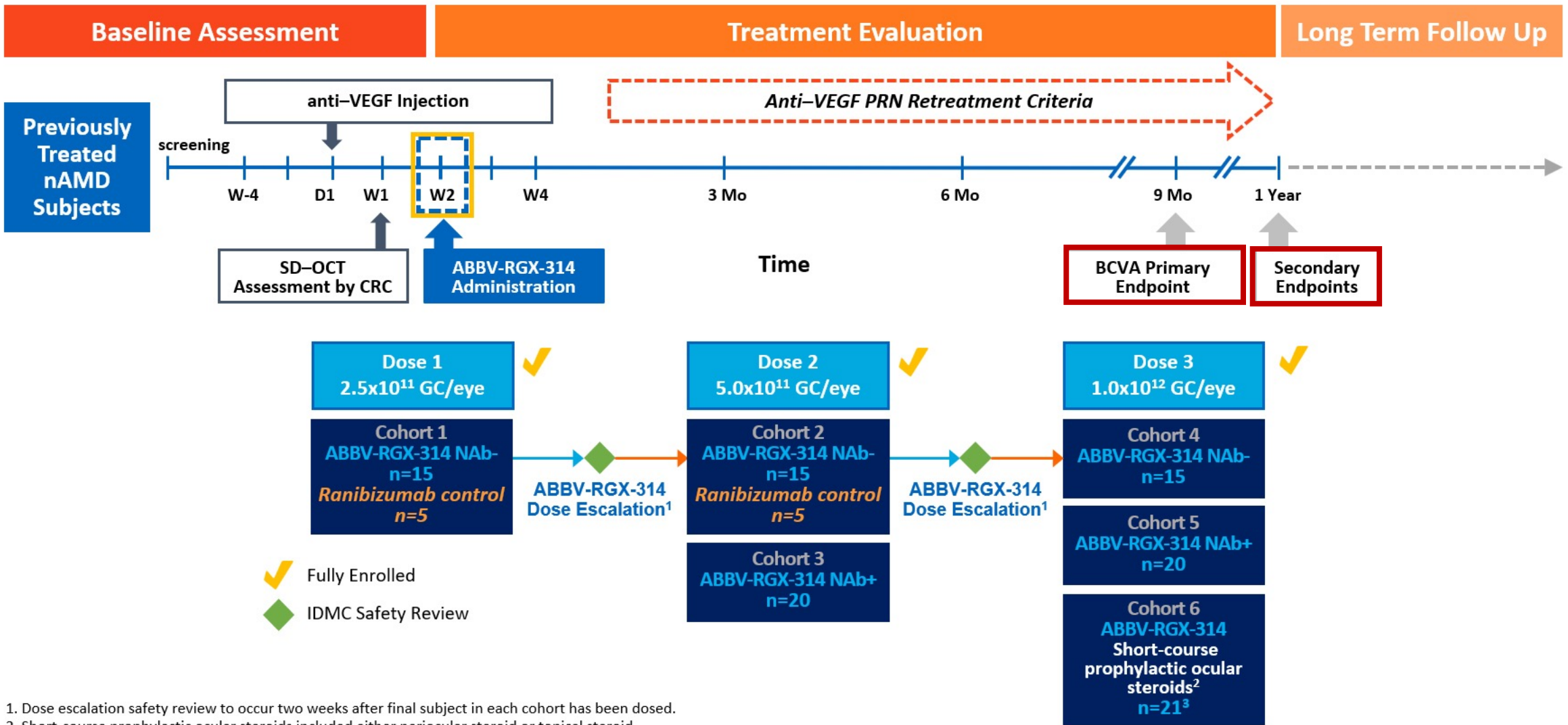
- In-office SCS Microinjector™ delivers ABBV-RGX-314 to the **suprachoroidal space**

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

Pitcher, Hawaiian Eye and Retina 2024

AAVIATE®: Study Design



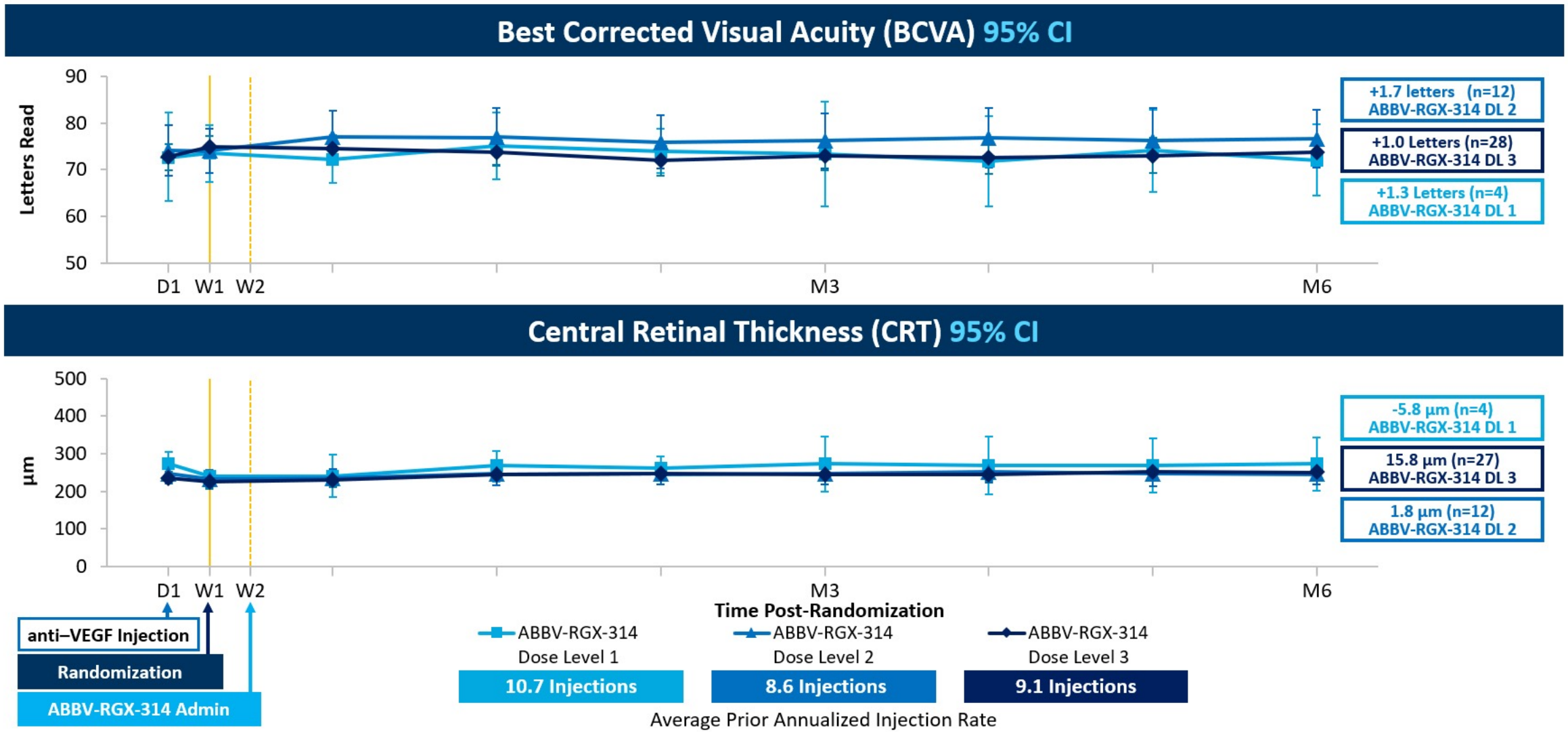
1. Dose escalation safety review to occur two weeks after final subject in each cohort has been dosed.
2. Short-course prophylactic ocular steroids included either periocular steroid or topical steroid
3. Additional anti–VEGF Run-in Injections given at W-4 and W4

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

Pitcher, Hawaiian Eye and Retina 2024

Dose Levels 1–3: No Anti-VEGF Injections over 6 Months

Mean BCVA and CRT from Day 1

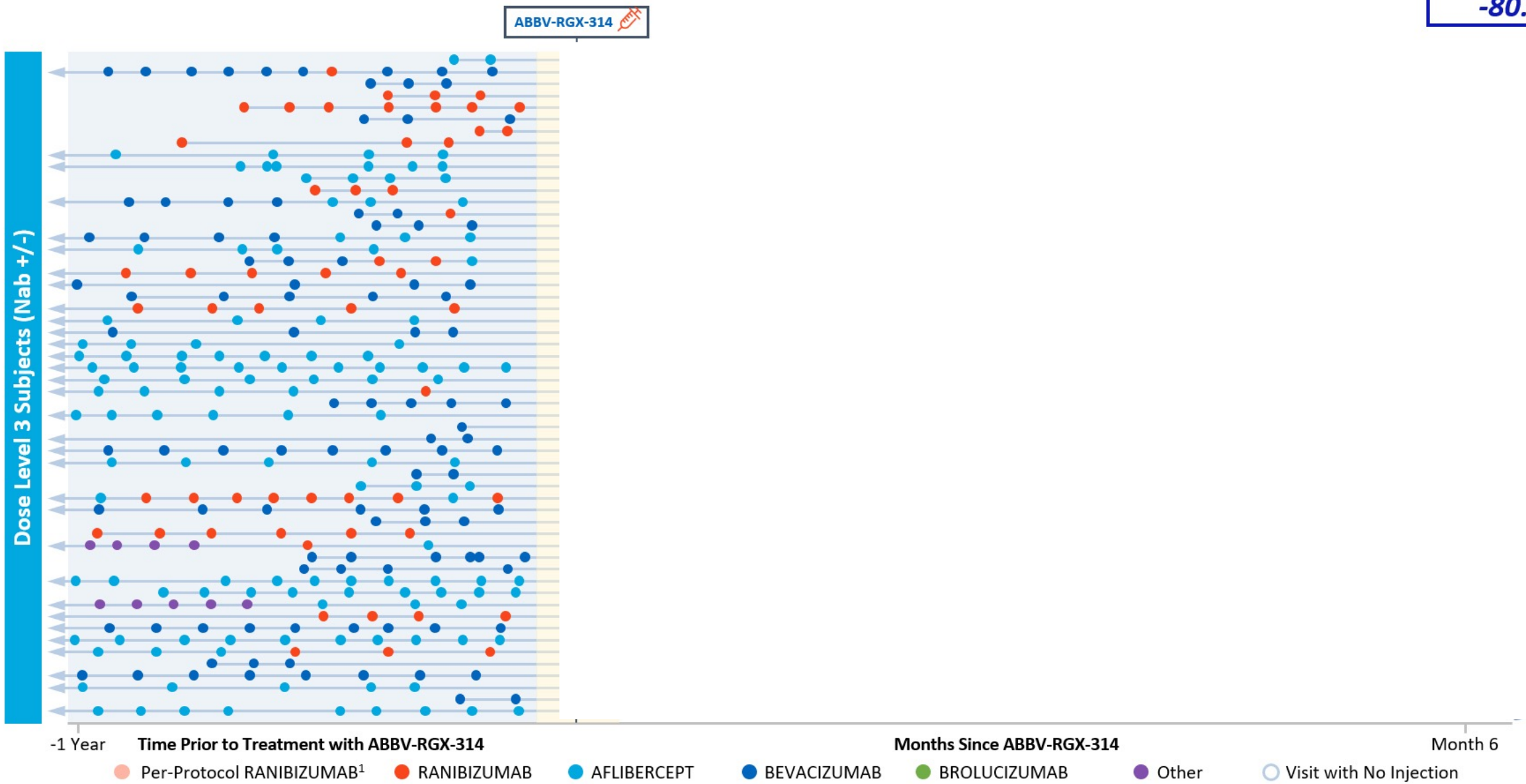


Data cut: November 06, 2023. Cohort 6 (DL3) patients were randomized at D1 and received additional anti–VEGF run-in injections at W-4 and W4.

Pitcher, Hawaiian Eye and Retina 2024

Dose Level 3: Injections Pre and Post ABBV-RGX-314 (n=56) – 6 Month Data

Change in Annualized Injection Rate -80.0%



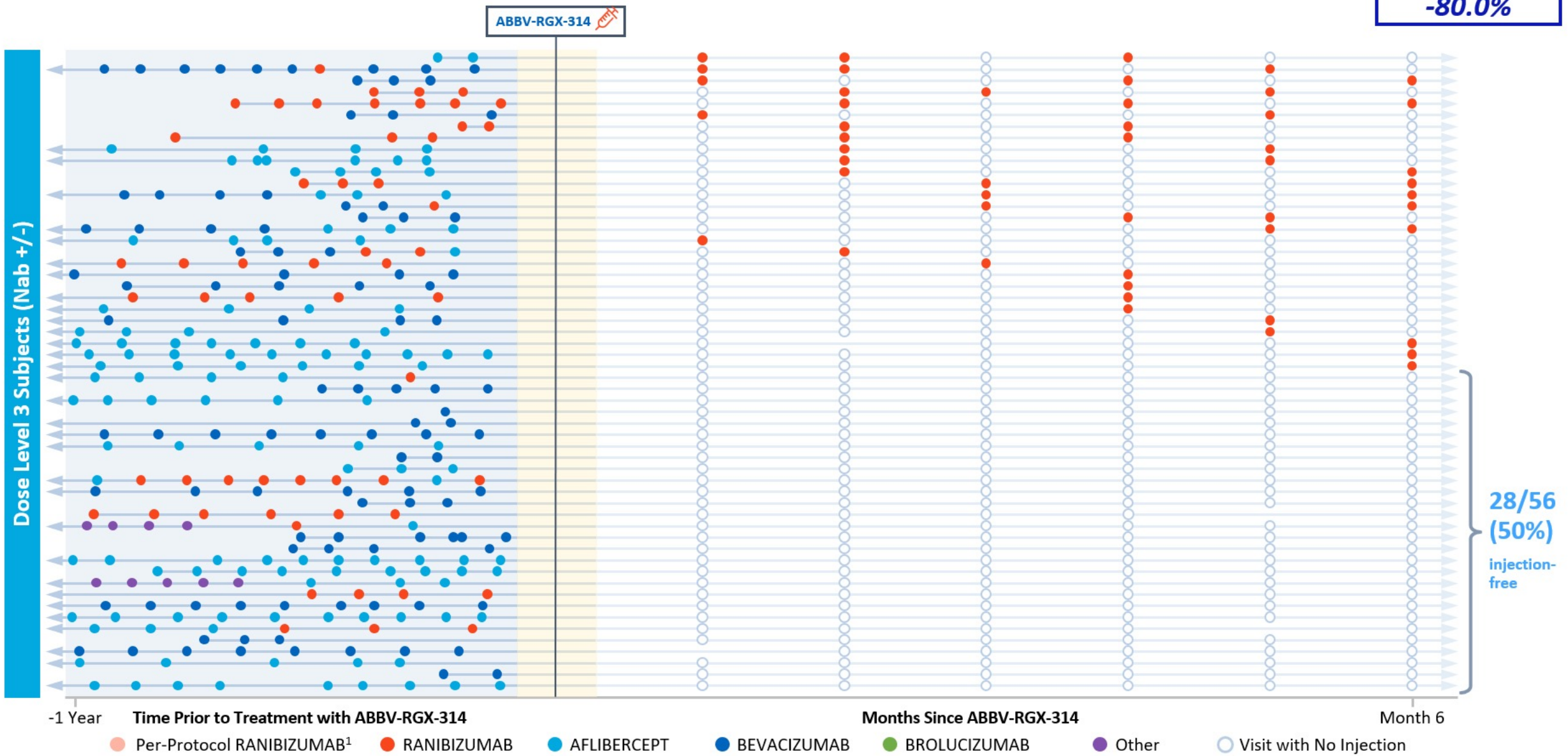
Data cut: November 06, 2023.

1. Protocol specified Ranibizumab injections included either 1 run-in injection or 2 run-in injections and 1 post ABBV-RGX-314 injection.

Pitcher, Hawaiian Eye and Retina 2024

Dose Level 3: Injections Pre and Post ABBV-RGX-314 (n=56) – 6 Month Data

Change in Annualized Injection Rate
-80.0%



Data cut: November 06, 2023.
1. Protocol specified Ranibizumab injections included either 1 run-in injection or 2 run-in injections and 1 post ABBV-RGX-314 injection.

Pitcher, Hawaiian Eye and Retina 2024

Summary of Interim Results from the Phase II AAVIATE® nAMD Study

ABBV-RGX-314 Dose Levels 1-3 (n=106): 6 Month Results

- Suprachoroidal ABBV-RGX-314 has been well-tolerated
- **Zero cases of IOI** in subset of Dose Level 3 with short-course prophylactic topical steroids
- **ABBV-RGX-314 continues to demonstrate stable vision and retinal thickness, with a meaningful reduction in treatment burden with the highest reduction seen in Dose Level 3:**
  - 80% reduction in annualized injection rate
  - 50% injection-free

Dose Level 3 continues to show encouraging interim results with a well-tolerated profile, including zero cases of IOI with short-course prophylactic topical steroids

Data cut: November 06, 2023.

Pitcher, Hawaiian Eye and Retina 2024

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

ABBV-RGX-314 is an investigational product that has not been approved by the FDA. No conclusions regarding the safety and efficacy of the product can be made.

V:13Nov23

ALTITUDE®: ABBV-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 ABBV-RGX-314
- Development of DR-related ocular complications
- Need for additional standard of care interventions

Subjects: 99 patients enrolled in Cohorts 1-5

- 79 ABBV-RGX-314; 20 observation control
- 21 study sites across the United States

Route of Administration

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

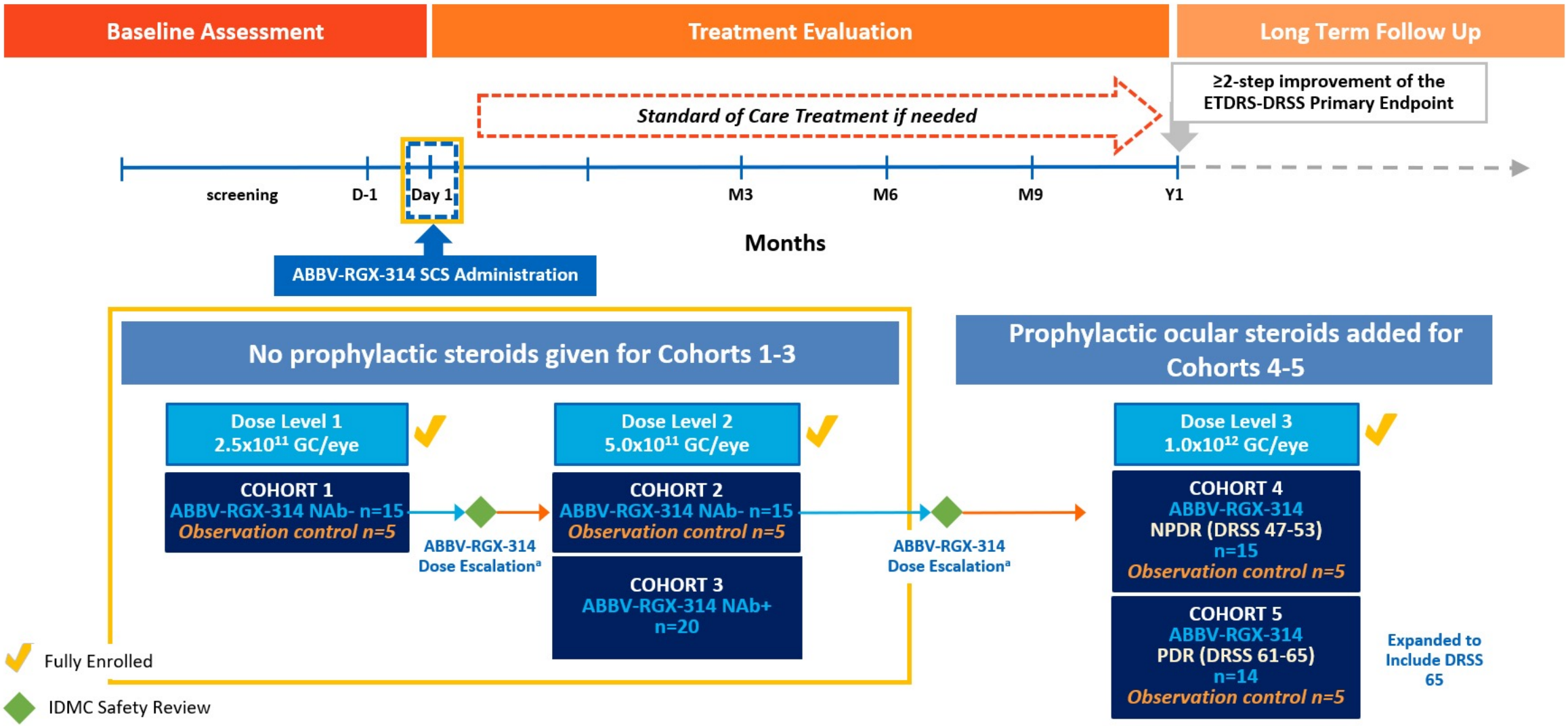
Key Inclusion Criteria

- 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 47-65)**
- 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

Khanani, Euretina 2023

ABBV-RGX-314 ALTITUDE® Study Design

Moderately Severe NPDR, Severe NPDR, or Mild PDR Patients without active CI-DME

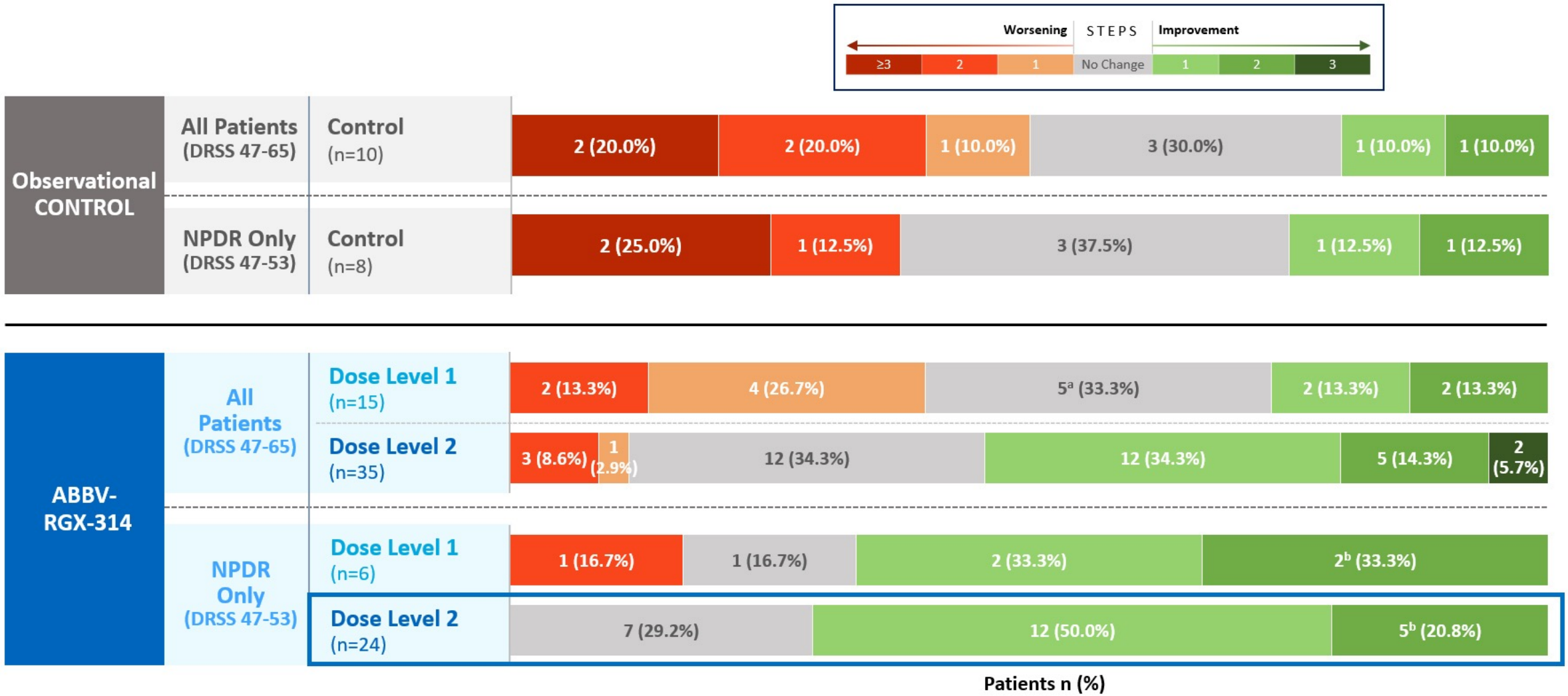


a. Dose escalation safety review to occur two weeks after final subject in each cohort has been dosed.

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

Barakat, AAO 2023

Summary of DRSS Change With Dose Levels 1 and 2 Compared to Control at 1 Year



Data cut: September 25, 2023.
a. During an interim central reading center masked adjudication, 1 patient's DRSS grade at baseline was updated from Grade 47 to Grade 65.
b. One patient in each Dose Level missed their 1-Year visit, so their 6-month results were used.

Barakat, AAO 2023

Summary of ABBV-RGX-314 1 Year Results from the Phase II ALTITUDE DR Study: Dose Level 1 and 2

- **Safety**
  - Suprachoroidal ABBV-RGX-314 continues to be **well-tolerated in Dose Levels 1 and 2 (n=50) through 1 Year**
  - No prophylactic corticosteroids administered in Dose Levels 1 and 2
  - A few cases of mild intraocular inflammation were observed; resolved with topical corticosteroids
- **Efficacy Endpoints**
  - **One-time in-office injection** of investigational ABBV-RGX-314 demonstrated clinically meaningful improvements in disease severity and reduction of VTEs in NPDR patients
  - **In Dose Level 2 patients with baseline NPDR (n=24):**
    - **100%** demonstrated stable to improved disease severity
      - 70.8% achieved any disease improvement vs. 25.0 % in Control
      - 0% worsened ≥2 steps vs. 37.5 % in Control
    - 4.2% developed VTEs vs. 37.5% in Control

Dose Level 2 prevented disease progression in all NPDR patients and reduced Vision-Threatening Events by 89%

Data cut: September 25, 2023.
VTEs: Vision-Threatening Events = VTCs + CI-DME

Barakat, AAO 2023

Multiple Partnerships Expand Utilization of Suprachoroidal Delivery Using the SCS Microinjector

SCS Microinjector® Partner Clinical Development Programs

THERAPEUTIC	TYPE	INDICATION	IND-ENABLING	PHASE 1	PHASE 2	PHASE 3	APPROVAL
Bel-Sar	Virus-like Drug Conjugate	Choroidal Melanoma				CoMpas	
ABBV-RGX-314	AAV Gene Therapy	Diabetic Retinopathy w/o DME				ALTITUDE	
ABBV-RGX-314	AAV Gene Therapy	Wet AMD				AAVIATE	
Avoralstat	Plasma Kallikrein Inhibitor	DME					

Ocular Oncology

belzupacap sarotalocan

2024: Actively enrolling Phase 3

Gene Therapy

adeno-associated virus-based gene therapy

Q4 2024:

- Wet AMD: Enrolling new cohort at dose level 4
- DME: Enrolling new cohort at dose level 4

1H 2025: Initiate global pivotal trial in DR

Plasma Kallikrein Inhibitor

- **2024:** Conduct formulation and nonclinical work
- **2025:** Begin clinical trials


감사합니다
Natick
Grazie
Danke
Ευχαριστίες
Dalu
Thank You
Köszönöm
Obrigado
Tack
Спасибо
Dank
Gracias
谢谢
Merci
Seé
ありがとう
UT Southwestern
William P. Clements Jr.
University Hospital