ADVERUM BIOTECHNOLOGIES

Virtual IR/KOL Event

August 10, 2020

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Virtual IR/KOL Event Agenda

Time	Presentation	Speaker
10-minutes	Welcome	**Laurent Fischer, M.D.** CEO, Adverum Biotechnologies
30-minutes	OPTIC Presentation INFINITY DME Clinical Trial Design	**Arshad M. Khanani, M.D., M.A.** Managing Partner and Director of Clinical Research, Sierra Eye Associates, and Clinical Associate Professor of Ophthalmology, University of Nevada; Principal Investigator in OPTIC and INFINITY Trials
30-minutes	Q&A	Laurent Fischer, M.D. - CEO Aaron Osborne, MBBS - CMO Leone Patterson - President Thomas Leung - CFO Arshad M. Khanani, M.D., M.A., PI
5-minutes	Closing remarks	**Laurent Fischer, M.D.**

ADVERUM BIOTECHNOLOGIES

Phase 1 Study of Intravitreal Gene Therapy with ADVM-022 for Neovascular Age-related Macular Degeneration (OPTIC Trial Cohorts 1-4)

Arshad M Khanani, M.D., M.A.

Director of Clinical Research, Sierra Eye Associates

(on behalf of the OPTIC investigators)

OPTIC

Gene Therapy in nAMD

August 10, 2020

Disclosures

- **Grant Support:** Adverum, Allergan, Chengdu Kanghong, Genentech, Gyroscope, Gemini Therapeutics, Kodiak, Novartis, Iveric Bio, Opthea, Oxurion, Recens Medical, Roche, Regenxbio
- **Consultant:** Adverum, Allergan, Bausch and Lomb, Chengdu Kanghong, Eyepoint Pharmaceuticals, Genentech, Gyroscope, Gemini Therapeutics, Kodiak, Novartis, Opthea, Oxurion, Recens Medical, Regenxbio
- **Speaker:** Allergan, Novartis

Key Takeaways for ADVM-022

- Continues to show robust treatment response
- Long-term durability beyond 15 months from single IVT injection with zero rescue injections in Cohort 1
- Further evidence of a dose response between the high and low doses
- Substantial reduction in annualized anti-VEGF injection frequency
- Continues to be well tolerated with a favorable safety profile in all 4 cohorts including encouraging early safety data from Cohort 4 using prophylactic steroid eye drops
- Warrants further investigation in larger studies

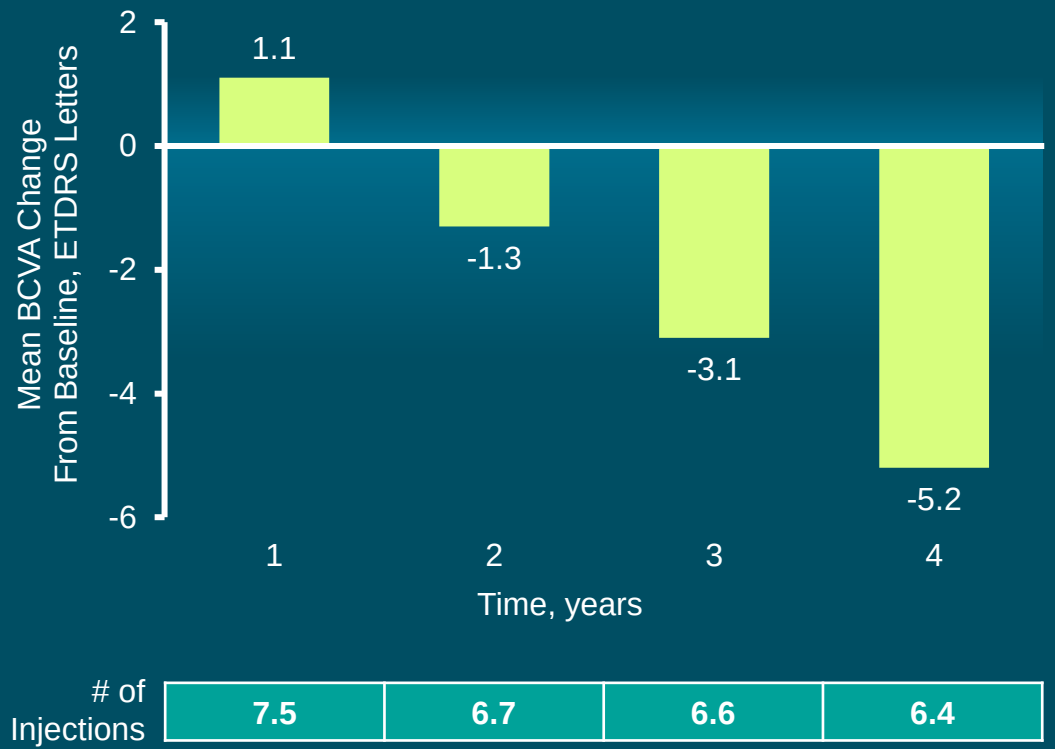
AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; CST, central subfield thickness; VEGF, vascular endothelial growth factor; IVT, intravitreal

Data cut: July 23, 2020

Real-world anti-VEGF Patient Outcomes

Under treatment leads to vision loss over time

98,821 Eyes from 79,885 US Patients Receiving Routine Intravitreal anti-VEGF Therapy



Development Approach to Deliver Long-Term Efficacy

Gene Therapy

In-Office Intravitreal Injection to Establish an Intraocular anti-VEGF Biofactory

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study
IVT, intravitreal therapy; VEGF, vascular endothelial growth factor

Khanani AM, et al. Ophthalmology Retina 2020;4:122-13

ADVM-022: Adeno-Associated Virus Gene Therapy Vector

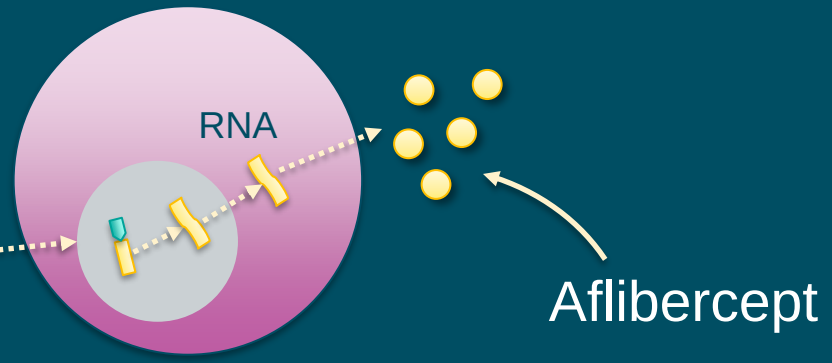
Designed for continuous delivery of aflibercept by intravitreal injection

AAV.7m8 capsid

Capsid Engineered from Wild-Type AAV2 by Directed Evolution and Screened for Highly Efficient Retinal Transduction Following IVT Injection

Aflibercept Expression Cassette

Strong, Ubiquitous Promoter Designed for Robust Protein Expression



Target Retinal Cell Expresses Aflibercept

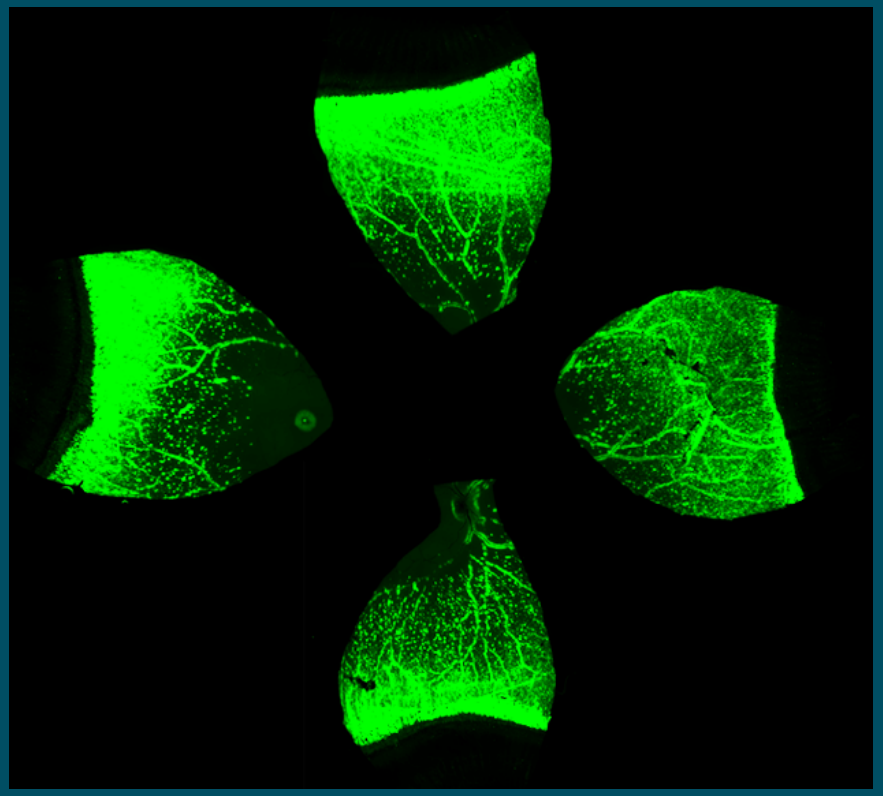
Codon-Optimized cDNA

IVT, Intravitreal

Grishanin, R et al. Mol Ther 2019;27:118–29

Intravitreal Injection of AAV.7m8 Results in Robust Cellular Transduction and Protein Expression in the Eye

- Advanced AAV.7m8 vector developed using directed evolution to:
  - Enable efficient intravitreal delivery[1,3]
  - Increase transduction of retinal cells[1,3]
  - Increase protein expression[1]
- Protein expression in NHPs:
  - Photoreceptors, ganglion cells[1-3]
  - Bipolar cells, Müller cells, optic nerve[2]
  - Ciliary epithelium, iris pigment epithelium[2]



Green Fluorescent Protein Expression In Non-Human Primate Retina[1]

1. Grishanin, R. et al. Mol. Ther. 2019;27:118–29
2. Ramachandran PS, et al. Hum Gene Ther 2017;28:154–67
3. Dalkara, D. et al. Sci Transl Med 2013, 5:189ra76

NHP, non-human primate

Preclinical NHP Data Demonstrate Long-Term Sustained Aflibercept Levels Comparable to Aflibercept Bolus Injection

Two Studies: Stable Long-Term Protein Expression Up to 21 and 30 Months After Single ADVM-022 IVT Injection

**Time after IVT injection of bolus aflibercept protein (1.2 mg/eye; separate study) when similar aflibercept levels were observed in NHPs*
IVT, intravitreal therapy; NHP, non-human primate

1. Kiss, S. Ann Meeting of the Am Soc Gene Cell Ther; 2019, Washington, DC
2. Grishanin, R Ann Congress Eur Soc Gene Cell Ther; 2018, Lausanne, Switzerland

OPTIC: Phase 1, Two-Year Multicenter Dose-Ranging Study of ADVM-022 in Neovascular AMD

OPTIC Gene Therapy in nAMD

- **Primary Objective**
  - Assess the safety and tolerability of a single IVT injection of ADVM-022
- **Secondary Objective**
  - Evaluate vision (BCVA)
  - Evaluate anatomy (SD-OCT)
  - Assess the need for rescue therapy

Oral steroid prophylaxis*: Cohort 1 ($6x10^{11}$ vg/eye, n=6) and Cohort 2 ($2x10^{11}$ vg/eye, n=6)

Steroid eye drops prophylaxis**: Cohort 3 ($2x10^{11}$ vg/eye, n=9) and Cohort 4 ($6x10^{11}$ vg/eye, n=9)

Patients Receive Rescue Aflibercept (2 mg IVT) if *any* of the Following Criteria are Met:

1. Loss of ≥10 letters in BCVA from baseline that is attributed to intraretinal or subretinal fluid observed by the investigator
2. Increase in central subfield thickness >75 µm from baseline
3. Presence of vision-threatening hemorrhage due to AMD

**Subjects received prophylaxis of 60 mg oral prednisone for 6 days starting at Day –3 followed by 7-day taper.*

***Subjects receive prophylaxis of QID difluprednate eye drops for 3 weeks starting at Day 1 followed by a 3-week taper.*

BCVA, best-corrected visual acuity; IVT, intravitreal therapy; SD-OCT, spectral domain optical coherence tomography; QID, 4x/day

NCT03748784

Limited Impact of COVID-19 on OPTIC Clinical Trial

Adverum: OPTIC Clinical Trial

- **Recruitment for Cohort 4 successfully completed during COVID-19**
- **Limited and manageable number of missed visits related to COVID-19**
- **Implementation of remote visits and telemedicine assessments when necessary**

Highlights the Value of Continuous Delivery of Treatment for Chronic Retinal Diseases

OPTIC Update for Cohorts 1-4 as of July 23, 2020

	Cohort 1 (N=6)	Cohort 2 (N=6)	Cohort 3 (N=9)	Cohort 4* (N=9)
ADVM-022 Dose, vg/eye	**High Dose** 6×10^{11}	**Low Dose** 2×10^{11}	**Low Dose** 2×10^{11}	**High Dose** 6×10^{11}
Steroid Prophylaxis	**Oral** 13-day course	**Oral** 13-day course	**Eye drops** 6-week course	**Eye drops** 6-week course
Follow-Up, Weeks	64–84 weeks (median 72)	52–56 weeks (median 52)	20–40 weeks (median 36)	2–8 weeks (median 4)
Subject Disposition	No discontinuations, some visits missed due to COVID-19 concerns	No discontinuations	No discontinuations, some visits missed due to COVID-19 concerns	No discontinuations
Baseline Characteristics	✓	✓	✓	✓
Safety Data	✓	✓	✓	✓
Efficacy Data†	✓ No rescue injections	✓	✓	N/A* No rescue injections

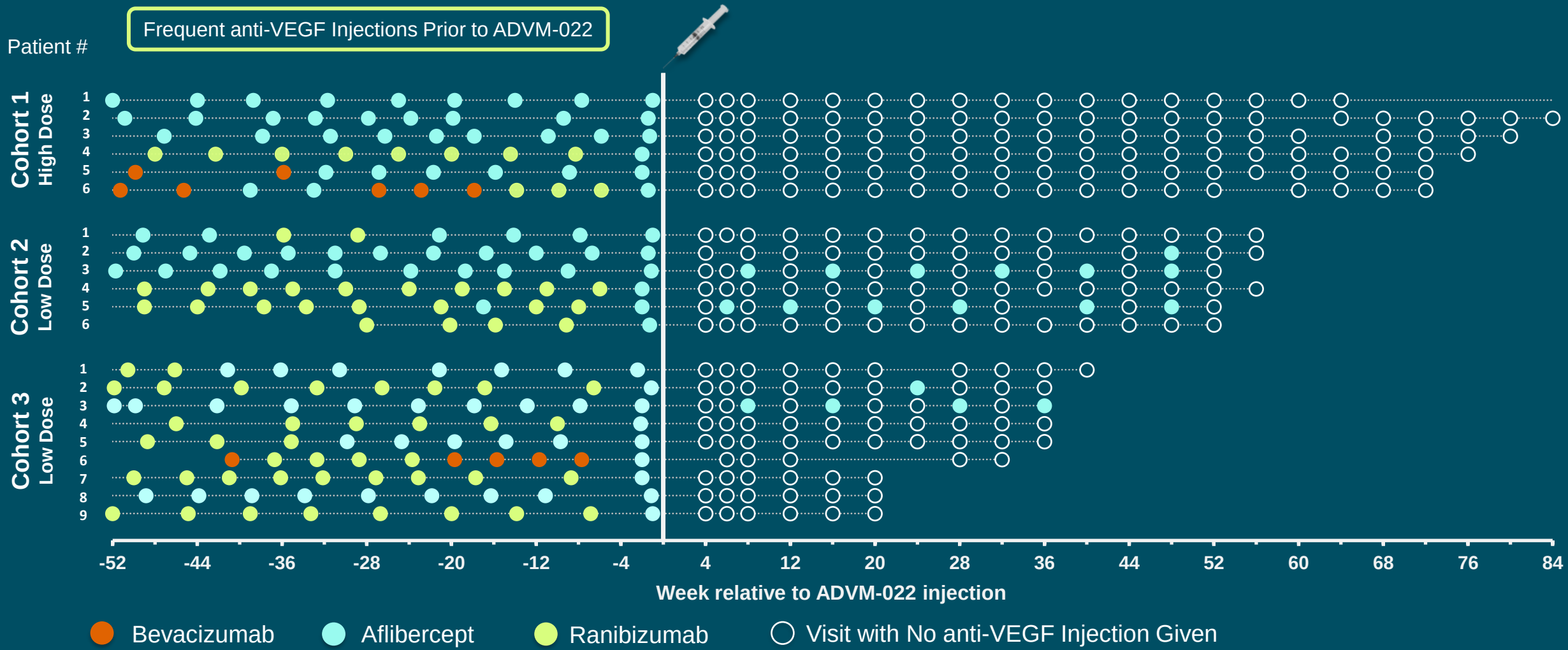
**Cohort 4 has short duration of follow-up, insufficient for assessment of efficacy*
†Includes BCVA and CST outcomes and need for rescue anti-VEGF

Neovascular AMD Study Population Previously Required Frequent Injections to Maintain Vision

Baseline Characteristics	Cohort 1 (N=6)	Cohort 2 (N=6)	Cohort 3 (N=9)	Cohort 4 (N=9)
Mean (range) Age, Years	79.0 (62–88)	79.8 (74–90)	77.4 (65–90)	79.9 (68–88)
Mean (range) Years Since nAMD Diagnosis	3.5 (0.9–10.6)	4.1 (0.5–6.8)	3.3 (0.7–8.0)	3.2 (0.2–8.0)
Mean (range) Number anti-VEGF Injections Since Initial Diagnosis*	32.2 (7–109)	34.0 (4–69)	24.8 (9–70)	28.5 (2–58)**
Mean (range) Number anti-VEGF Injections in 12 Months Prior to ADVM-022	9.2 (8–11)	9.2 (5–11)	9.1 (7–10)	6.8 (3–12)**
Mean (range) BCVA, ETDRS Letters Approximate Snellen Equivalent	65.8 (57–77) 20/50	64.7 (53–72) 20/50	65.9 (53–75) 20/50	65.0 (54–77) 20/50
Mean (range) CST, µm	369.2 (293–561)	307.7 (235–339)	473.4 (301–857)	398.6 (255–538)

**Not including the mandated aflibercept at Screening; **Excluding Patient #2 with incomplete prior anti-VEGF data due to relocation.*
BCVA, best corrected visual acuity: CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study
nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor

Substantial Reduction in anti-VEGF Treatments Following a Single IVT Injection of ADVM-022



Two patients (Cohort 1 subject 1 and Cohort 3 subject 6) missed two or more consecutive visits due to COVID-19 concerns

VEGF, vascular endothelial growth factor; IVT, Intravitreal

Data cut: July 23, 2020

Safety Summary Across Cohorts through July 23, 2020

- No ADVM-022-related non-ocular adverse events
  - No deaths or discontinuations in OPTIC
- When observed, inflammation has been responsive to and manageable with steroid eye drops
  - Minimal early inflammation with steroid eye drops prophylaxis in Cohort 3 and Cohort 4
- No clinical or fluorescein* evidence of posterior inflammation
  - No vasculitis, retinitis, choroiditis, vascular occlusions or endophthalmitis
- All ADVM-022-related ocular AEs were mild (78%) to moderate (22%)
  - One AE of special interest of moderate recurrent uveitis deemed to be related to ADVM-022 was responsive to steroid eye drops (Cohort 1)
- One unrelated ocular SAE of retinal detachment surgically repaired and resolved (Cohort 1)
- Two patients had mild AEs of IOP elevation that resolved
  - One patient had two mild IOP elevations (highest 24 mmHg) that were both treated with Combigan® eye drops
  - One case in a patient on Combigan® for ocular hypertension at baseline which resolved with no change to treatment

**Fluorescein angiography of posterior pole*
IOP, intraocular pressure; AEs, adverse events; SAEs, serious AEs

Adverse Events Across Cohorts as of July 23, 2020

ADVM-022 related events were mild (78%) or moderate (22%)

Adverse Events		Cohort 1 (N=6) 6×10^{11} vg/eye Oral steroids 13-day prophylaxis		Cohort 2 (N=6) 2×10^{11} vg/eye Oral steroids 13-day prophylaxis		Cohort 3 (N=9) 2×10^{11} vg/eye Steroid eye drops 6-week prophylaxis		Cohort 4 (N=9) 6×10^{11} vg/eye Steroid eye drops 6-week prophylaxis	
		Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Ocular	Serious	2	2*	0	0	0	0	0	0
	ADVM-022 Related**	6	30	5	21	5	14	5	12
	Total Ocular	6	51	5	32	8	26	7	15
Non-Ocular†	Serious ‡	1	1	0	0	2	2	0	0
	Total Non-Ocular†	5	18	6	7	4	9	1	1

* *Retinal detachment (unrelated to ADVM-022) and recurrent moderate uveitis (likely related to ADVM-022)*

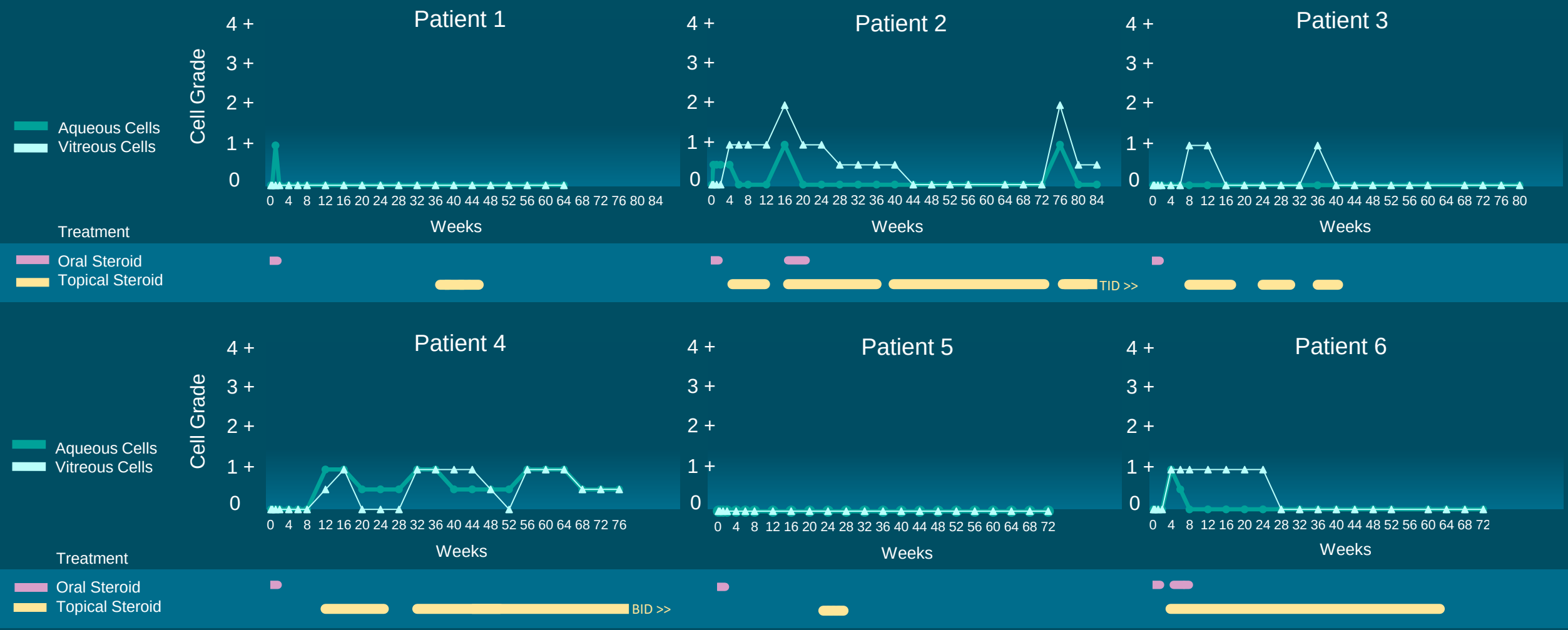
** *ADVM-022 related ocular events were mild (78%) or moderate (22%)*

† *None of the non-ocular AEs were ADVM-022 related*

‡ *Serious non-ocular AEs included degenerative intervertebral disc disease (1) in Cohort 1; and COPD exacerbation (1), and stable angina pectoris (1) in Cohort 3*

Cohort 1: Cellular inflammation as Assessed by Slit Lamp

Low grade and responsive to topical steroids

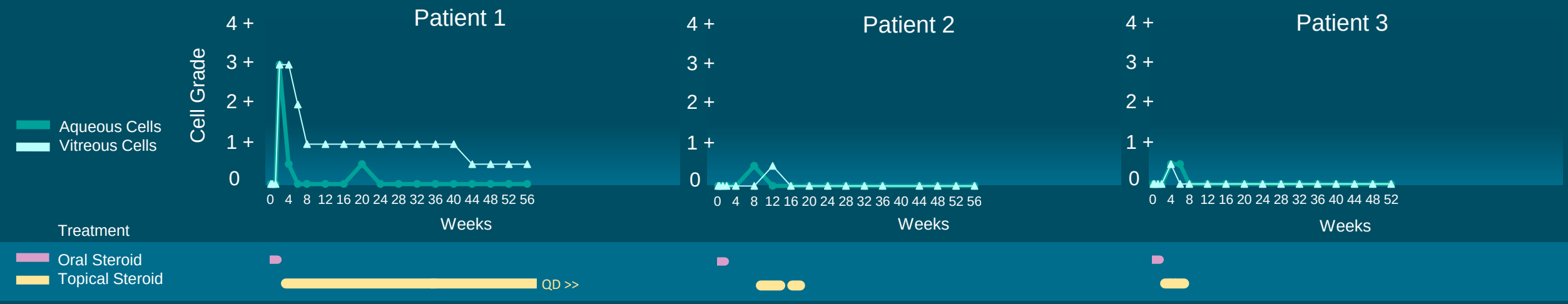


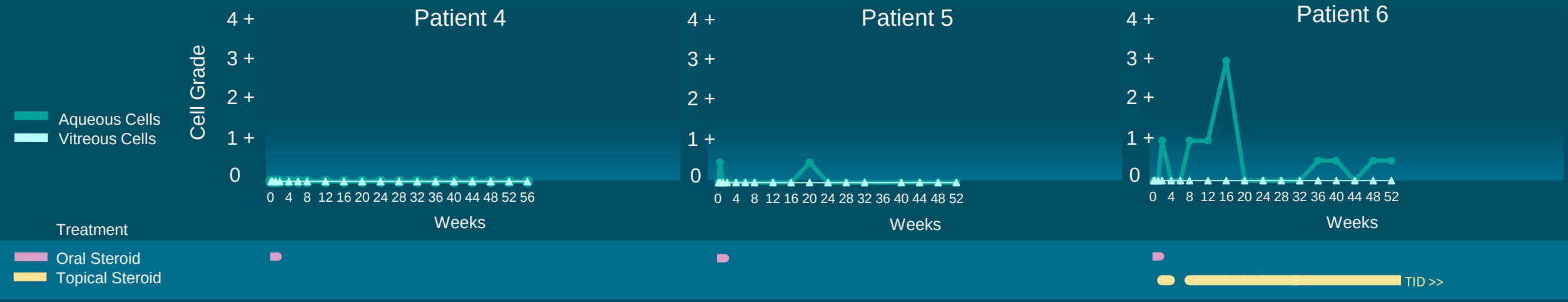
Aqueous cell grade categories are based on the Standardization of Uveitis Nomenclature (SUN) criteria: Jabs DA, et al. J Ophthalmol 2005;140:509–516
Vitreous cell grade categories are based on National Institutes of Health (NIH) guidelines
Aqueous cells: 0.5+: 1-5 cells 1+: 6-15 cells 2+: 16-25 cells 3+: 26-50 cells 4+: >50 cells
Vitreous cells: 0.5+: 1-10 cells 1+: 11-20 cells 2+: 21-30 cells 3+: 31-100 cells 4+: >100 cells; rare cells are captured as 0.5+ for this analysis

Data cut: July 23, 2020

Cohort 2: Cellular Inflammation as Assessed by Slit Lamp

Responsive to and managed with topical steroids





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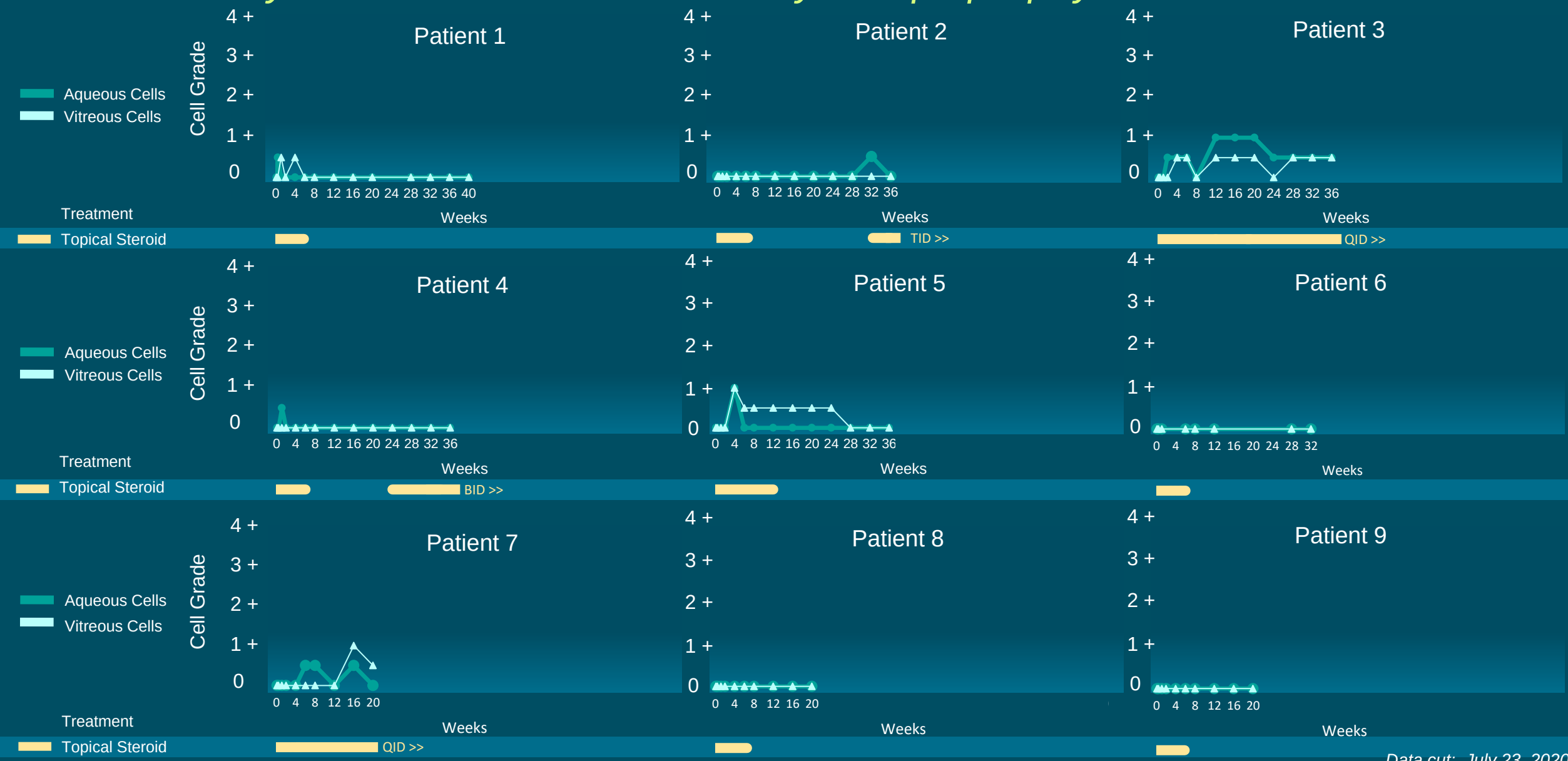
Vitreous cells: 0.5+: 1-10 cells 1+: 11-20 cells 2+: 21-30 cells 3+: 31-100 cells 4+: >100 cells; rare cells are captured as 0.5+ for this analysis

Data cut: July 23, 2020

Cohort 3: Cellular Inflammation as Assessed by Slit Lamp

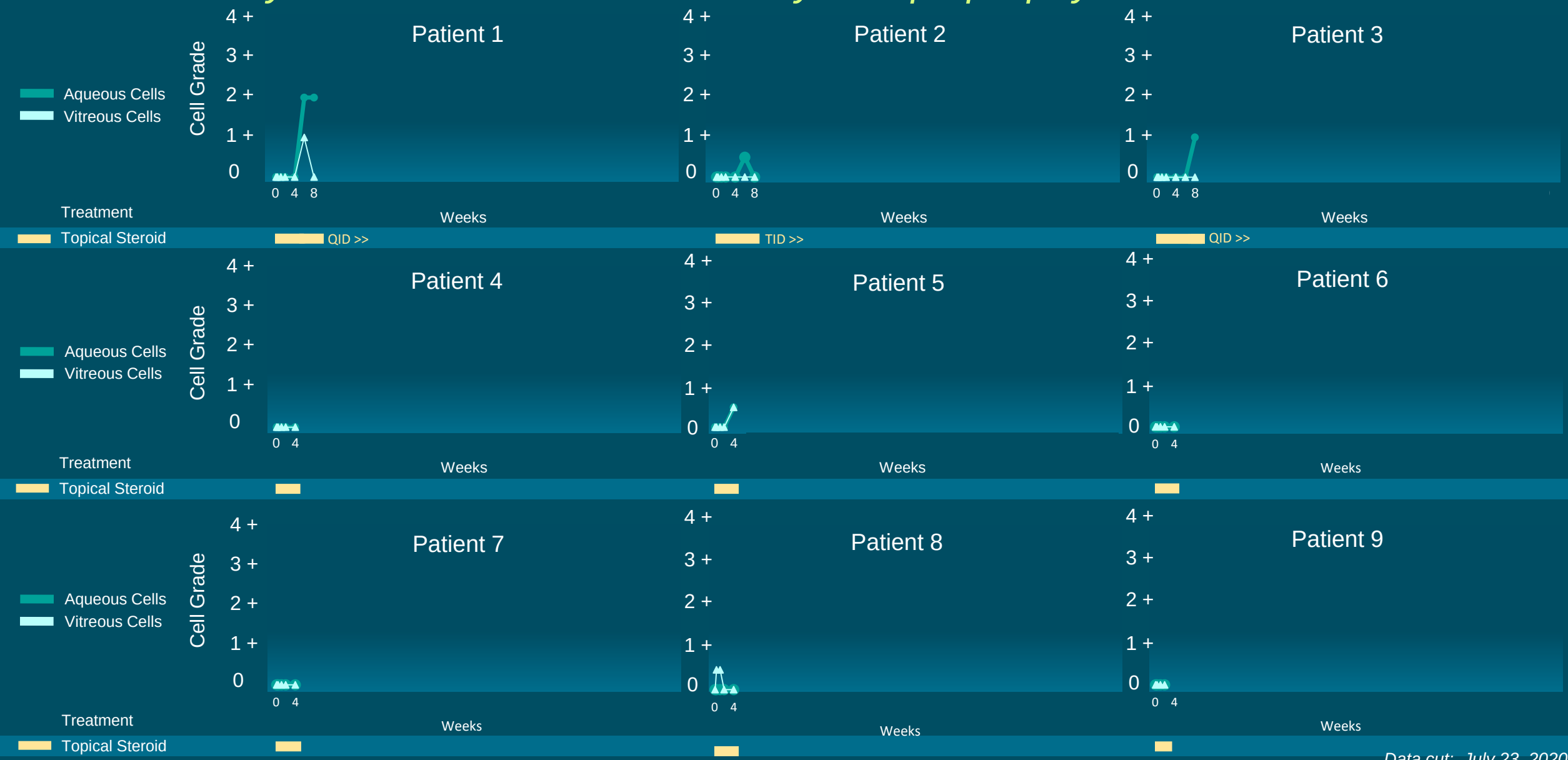
Minimal early inflammation with steroid eye drops prophylaxis



Data cut: July 23, 2020

Cohort 4: Cellular Inflammation as Assessed by Slit Lamp

Minimal early inflammation with steroid eye drops prophylaxis



Data cut: July 23, 2020

Cohort 1: BCVA Over Time

Mean (90% CI) by Visit Through Week 72

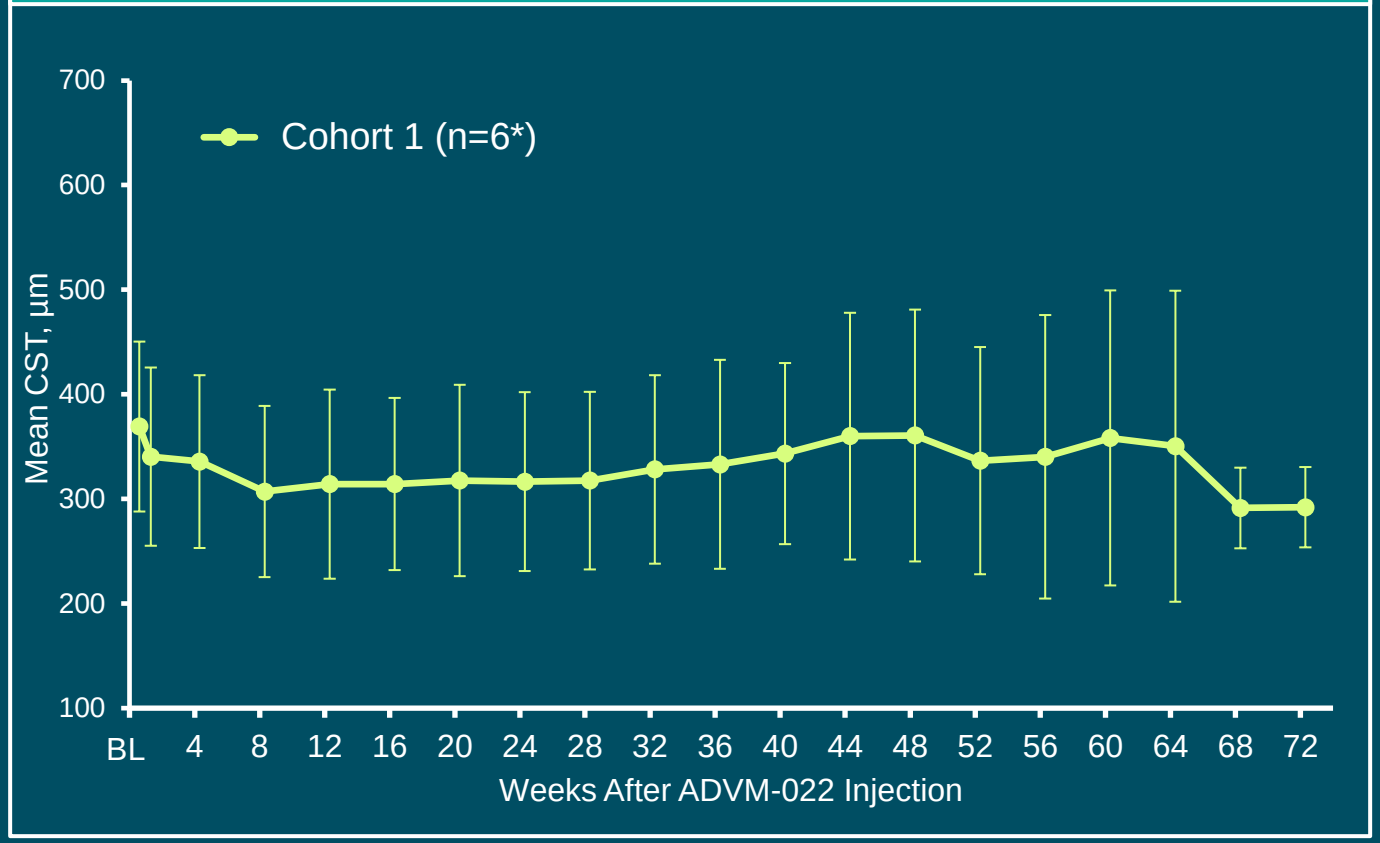
Latest Outcomes as of July 23, 2020

Follow-Up	64–84 weeks (median 72)
Rescue-Free Patients	100% (6/6)
Mean BCVA Change from Baseline	
All Patients	–3.2 Letters

**One patient had low BCVA score at 44 and 48 weeks due to retinal detachment; N=5 from Week 56 to 72*
Aflibercept 2 mg IVT administered at baseline, 7–15 days prior to ADVM-022 IVT (Day 1);
BCVA, best corrected visual acuity; CST, central subfield thickness; BL, baseline; D, day; W, week
Error bars are 90% CIs of the mean absolute BCVA and CST using T-distribution

Cohort 1: CST Over Time

Mean (90% CI) by Visit Through Week 72



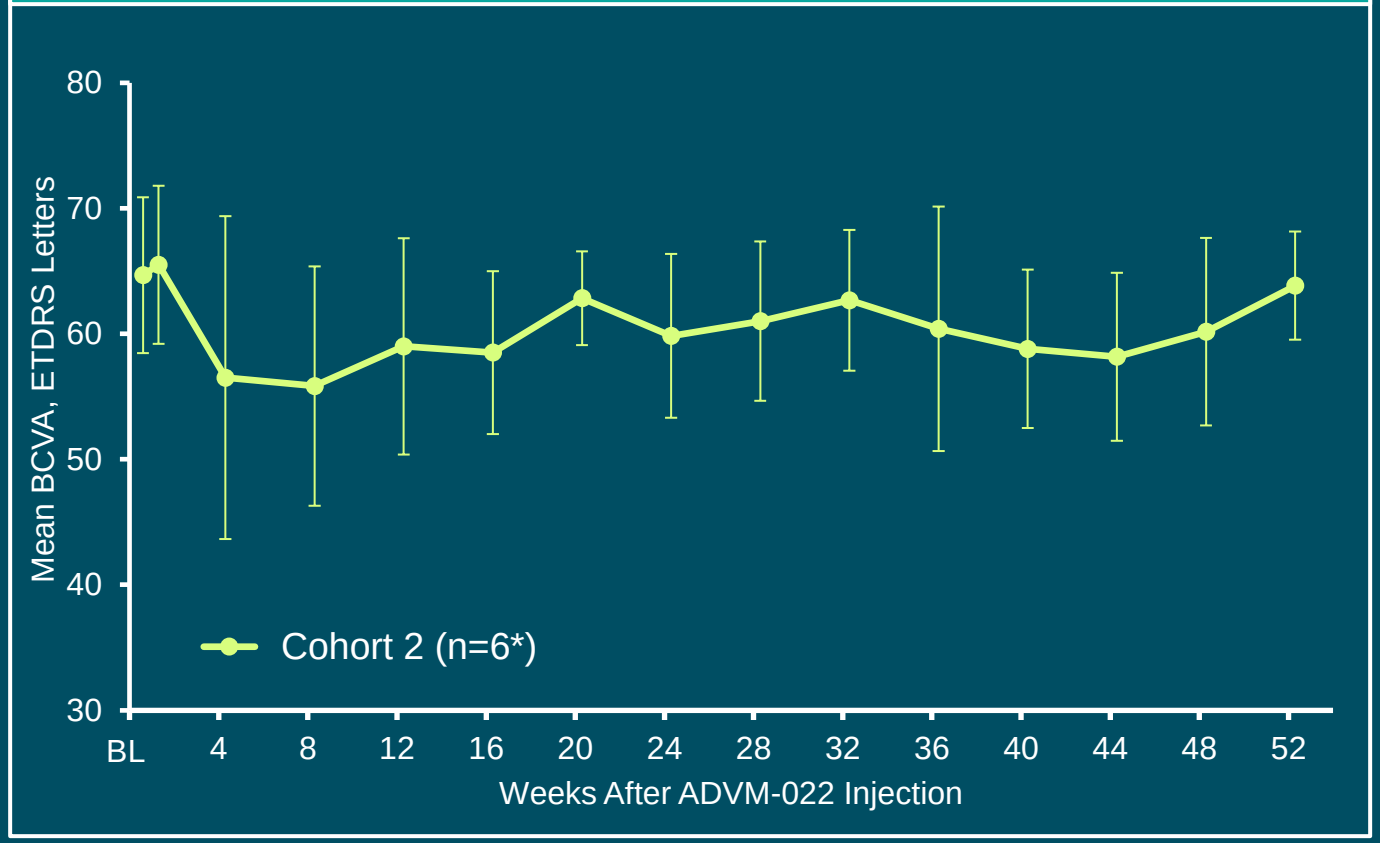
Latest Outcomes as of July 23, 2020

Follow-Up	64–84 weeks (median 72)
Rescue-Free Patients	100% (6/6)
Mean CST Change from Baseline	
All Patients	–21.0 µm

**One patient had no CST data at 44 and 48 weeks due to retinal detachment; N=5 from Week 56 to Week 72*
Aflibercept 2 mg IVT administered at baseline, 7–15 days prior to ADVM-022 IVT (Day 1);
BCVA, best corrected visual acuity; CST, central subfield thickness; BL, baseline; D, day; W, week
Error bars are 90% CIs of the mean absolute BCVA and CST using T-distribution

Cohort 2: BCVA Over Time

Mean (90% CI) by Visit Through Week 52



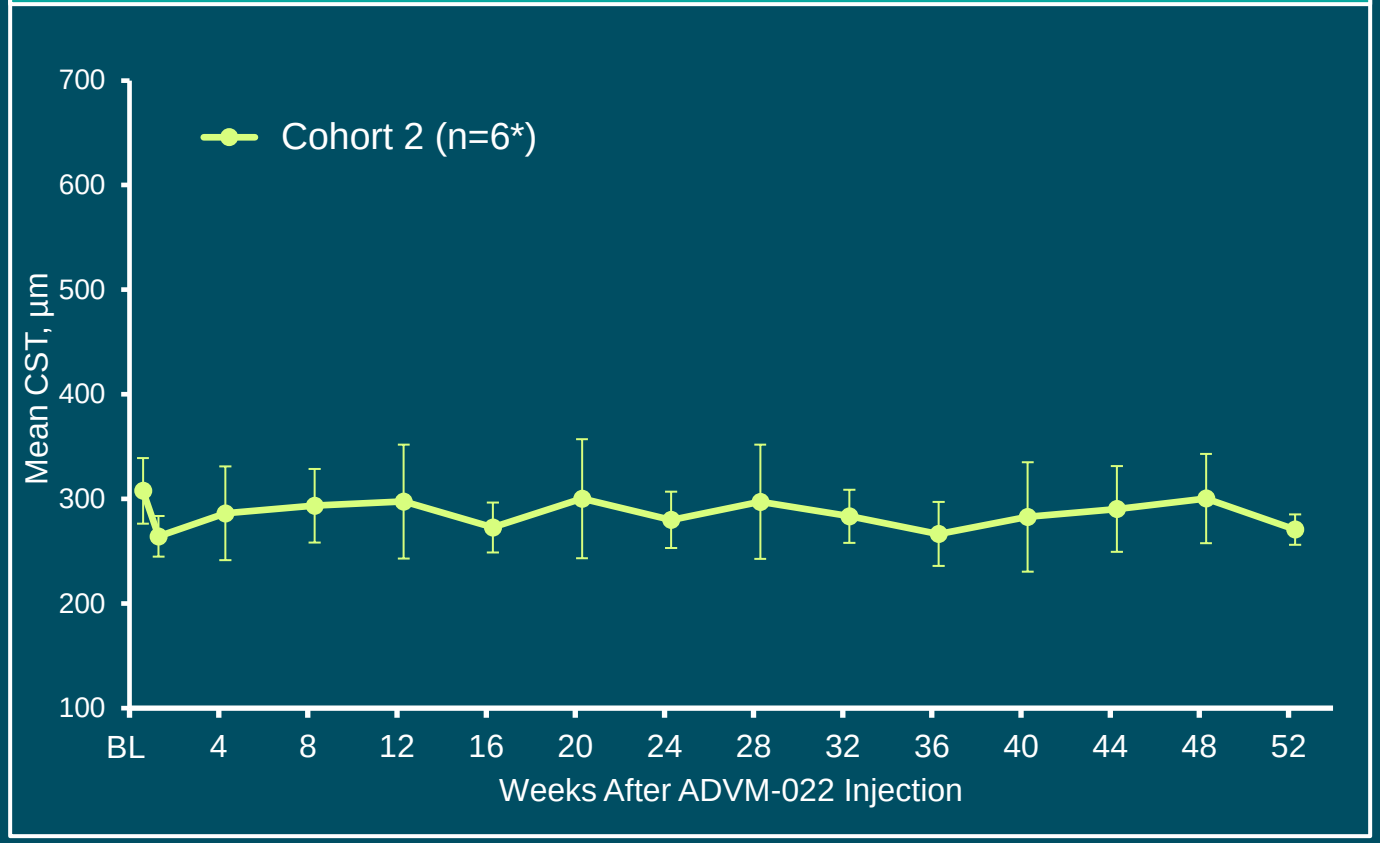
Latest Outcomes as of July 23, 2020

Follow-Up	52–56 weeks (median 52)
Rescue-Free Patients	50% (3/6)
Mean BCVA Change from Baseline:	
All Patients	–2.0 Letters
Rescue-Free Patients	+0 Letters

*Aflibercept 2 mg IVT administered at baseline, 7–15 days prior to ADVM-022 IVT (Day 1); *N=5 for Week 36 and 40 visit.*
BCVA, best corrected visual acuity; CST, central subfield thickness; BL, baseline; D, day; W, week
Error bars are 90% CIs of the mean absolute BCVA and CST using T-distribution

Cohort 2: CST Over Time

Mean (90% CI) by Visit Through Week 52



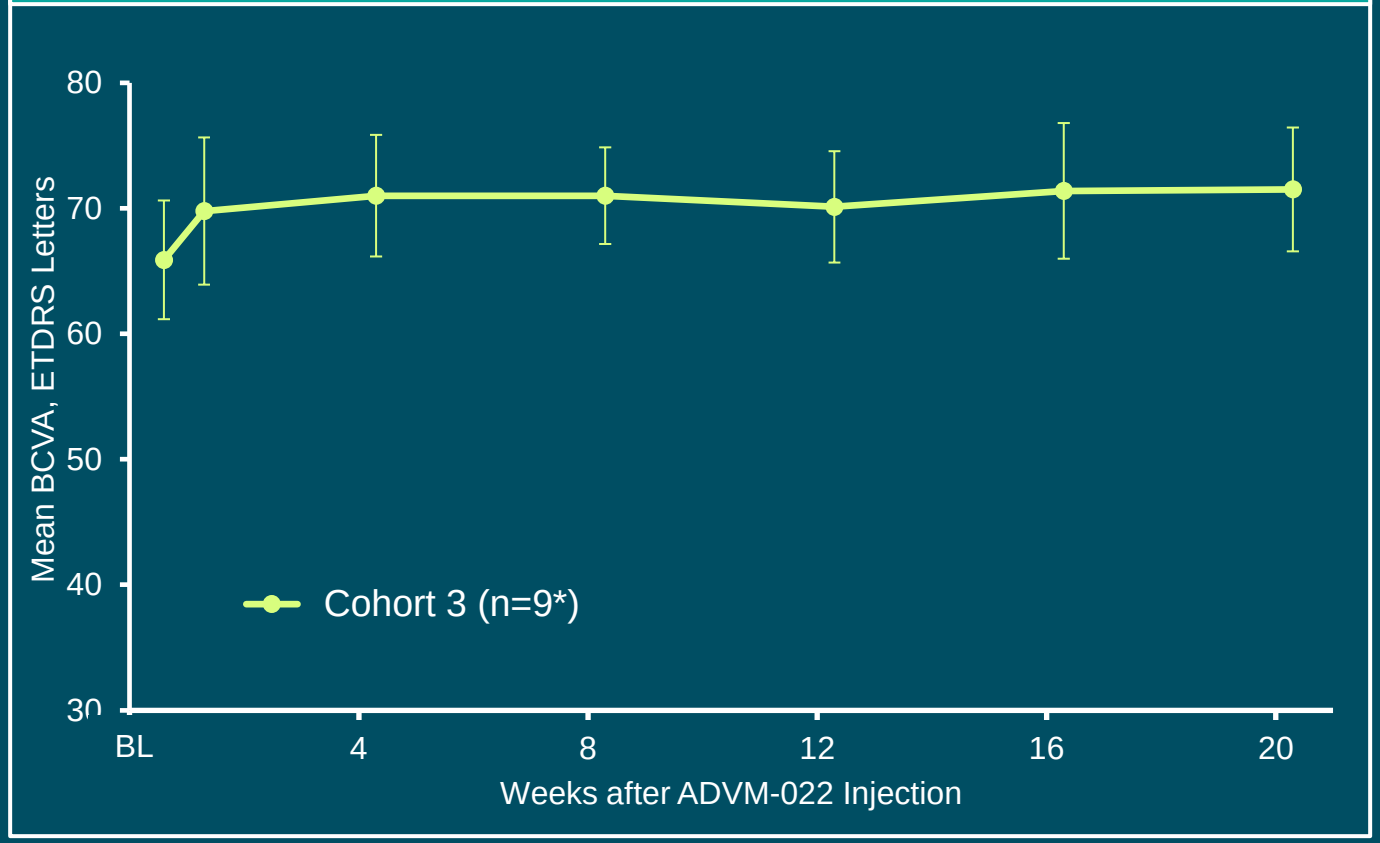
Latest Outcomes as of July 23, 2020

Follow-Up	52–56 weeks (median 52)
Rescue-Free Patients	50% (3/6)
Mean CST Change from Baseline:	
All Patients	–24.8 µm
Rescue-Free Patients	–8.3 µm

*Aflibercept 2 mg IVT administered at baseline, 7–15 days prior to ADVM-022 IVT (Day 1); *N=5 for Week 36 and 40 visit*
BCVA, best corrected visual acuity; CST, central subfield thickness; BL, baseline; D, day; W, week
Error bars are 90% CIs of the mean absolute BCVA and CST using T-distribution

Cohort 3: BCVA Over Time

Mean (90% CI) by Visit Through Week 20

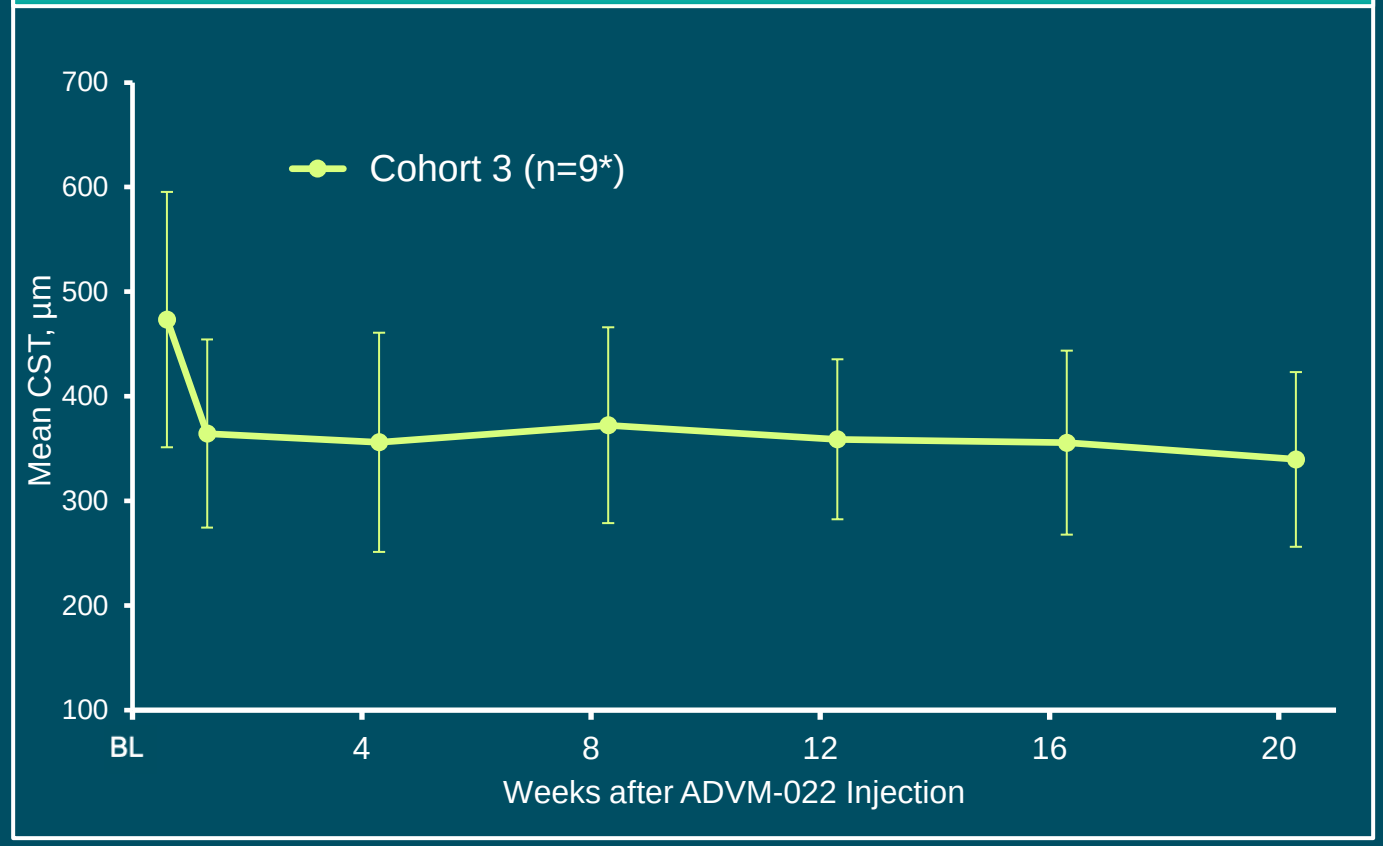


Latest Outcomes as of July 23, 2020	
Follow-Up	20–40 weeks (median 36)
Rescue-Free Patients	78% (7/9)
Mean BCVA Change from Baseline:	
All Patients	+4.0 Letters
Rescue-Free Patients	+6.4 Letters

**N=8 for Week 4, 16 and 20*
Aflibercept 2 mg IVT administered at baseline, 7–15 days prior to ADVM-022 IVT (Day 1)
BCVA, best corrected visual acuity; CST, central subfield thickness; BL, baseline; D, day; W, week
Error bars are 90% CIs of the mean absolute BCVA and CST using T-distribution

Cohort 3: CST Over Time

Mean (90% CI) by Visit Through Week 20



Latest Outcomes as of July 23, 2020

Follow-Up	20–40 weeks (median 36)
Rescue-Free Patients	78% (7/9)
Mean CST Change from Baseline:	
All Patients	–118.6 µm
Rescue-Free Patients	–152.7 µm

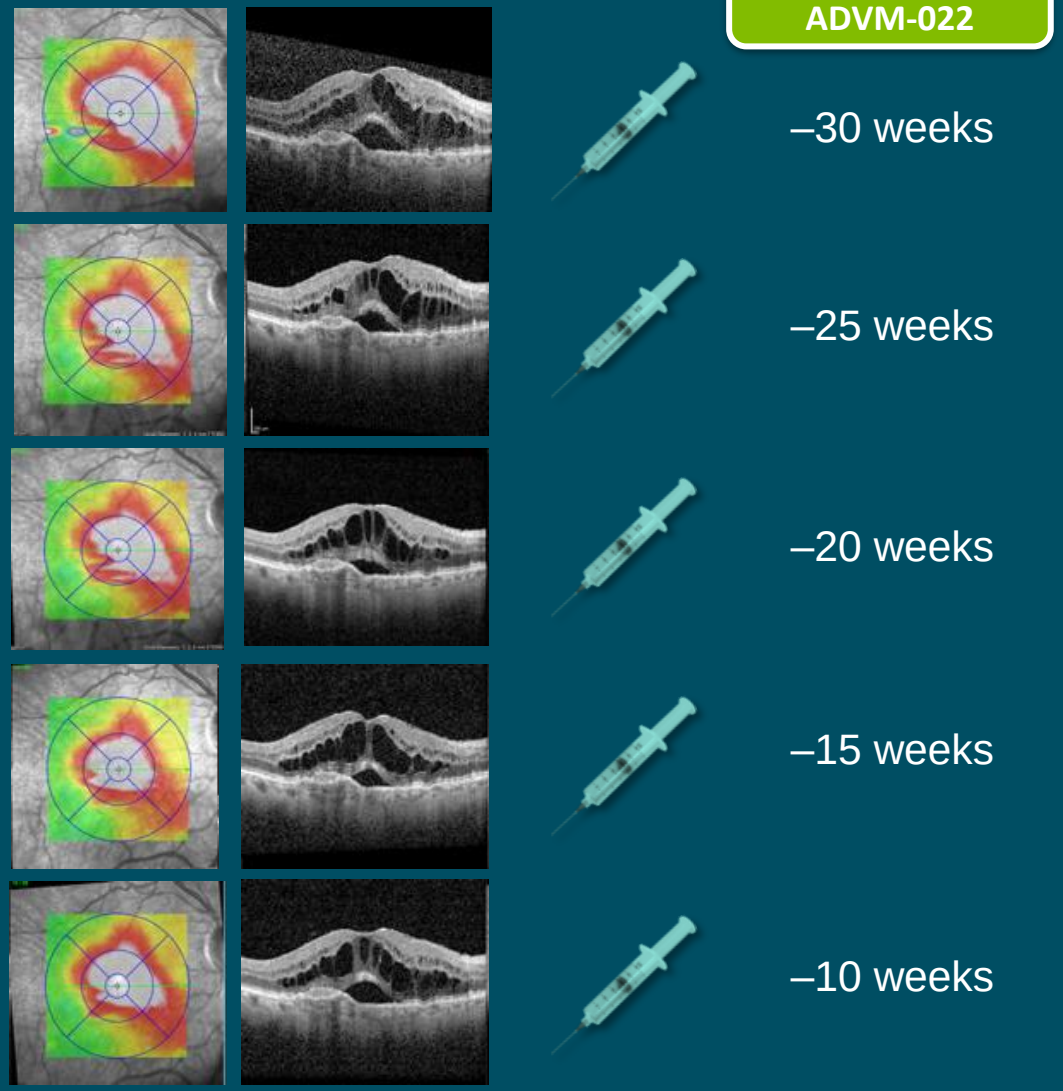
N=8 for Week 4, 16 and 20
Aflibercept 2 mg IVT administered at baseline, 7–15 days prior to ADVM-022 IVT (Day 1)
BCVA, best corrected visual acuity; CST, central subfield thickness; BL, baseline; D, day; W, week
Error bars are 90% CIs of the mean absolute BCVA and CST using T-distribution

Case Study: Cohort 3, Subject 5

Persistent fluid despite frequent anti-VEGF injections

OCT scans and treatment intervals from most recent 5 anti-VEGF injections visits prior to OPTIC

82 Year Old Male	
Previous IVT, n	19
IVT in Last 12 Months, n	9



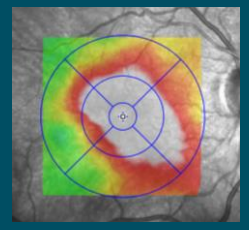
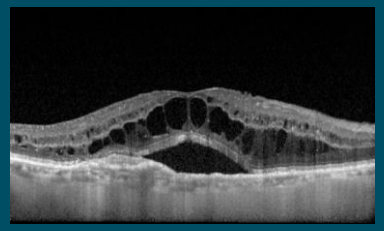
Aflibercept injections

IVT, intravitreal therapy; OCT, optical coherence tomography; VEGF, vascular endothelial growth factor

Case Study: Cohort 3, Subject 5

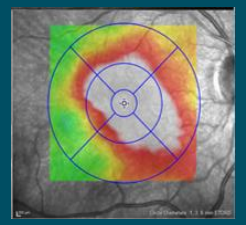
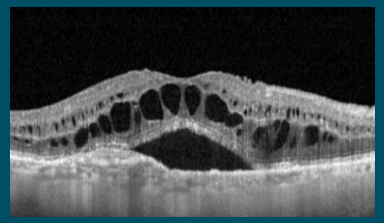
Rapid and sustained anatomical improvements

–3 weeks
Screening
BCVA: 77 letters
CST: 678 µm

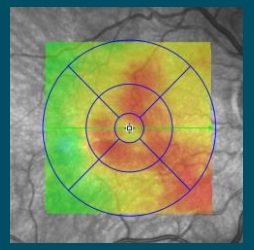
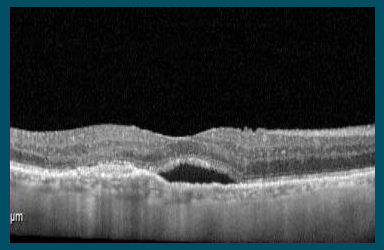
Aflibercept IVT

–2 weeks
BCVA: 75 letters
CST: 664 µm

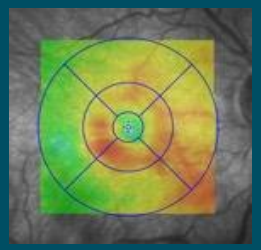
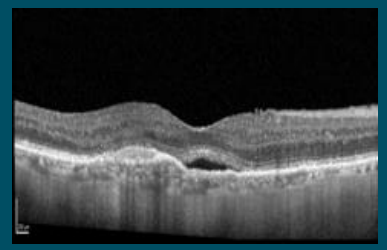



ADVM-022

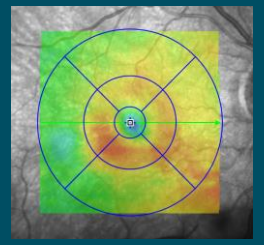
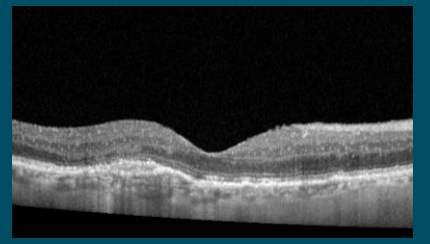
0 weeks
BCVA: 82 letters
CST: 355 µm

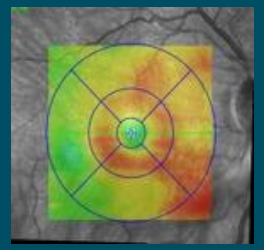
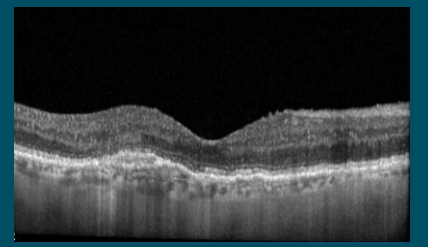
+1 week
BCVA: 80 letters
CST: 338 µm

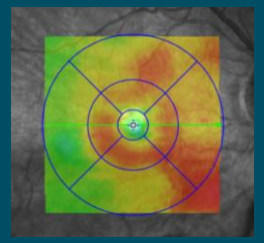
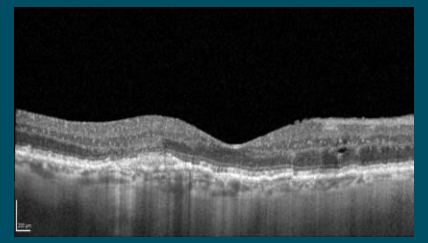
+12 weeks
BCVA: 81 letters
CST: 257 µm

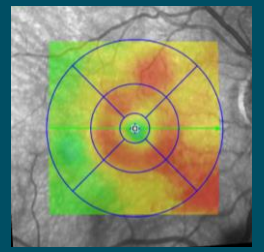
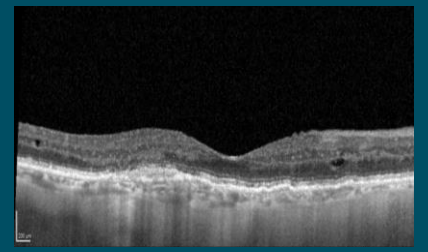
+20 weeks
BCVA: 82 letters
CST: 266 µm

+28 weeks
BCVA: 84 letters
CST: 277 µm

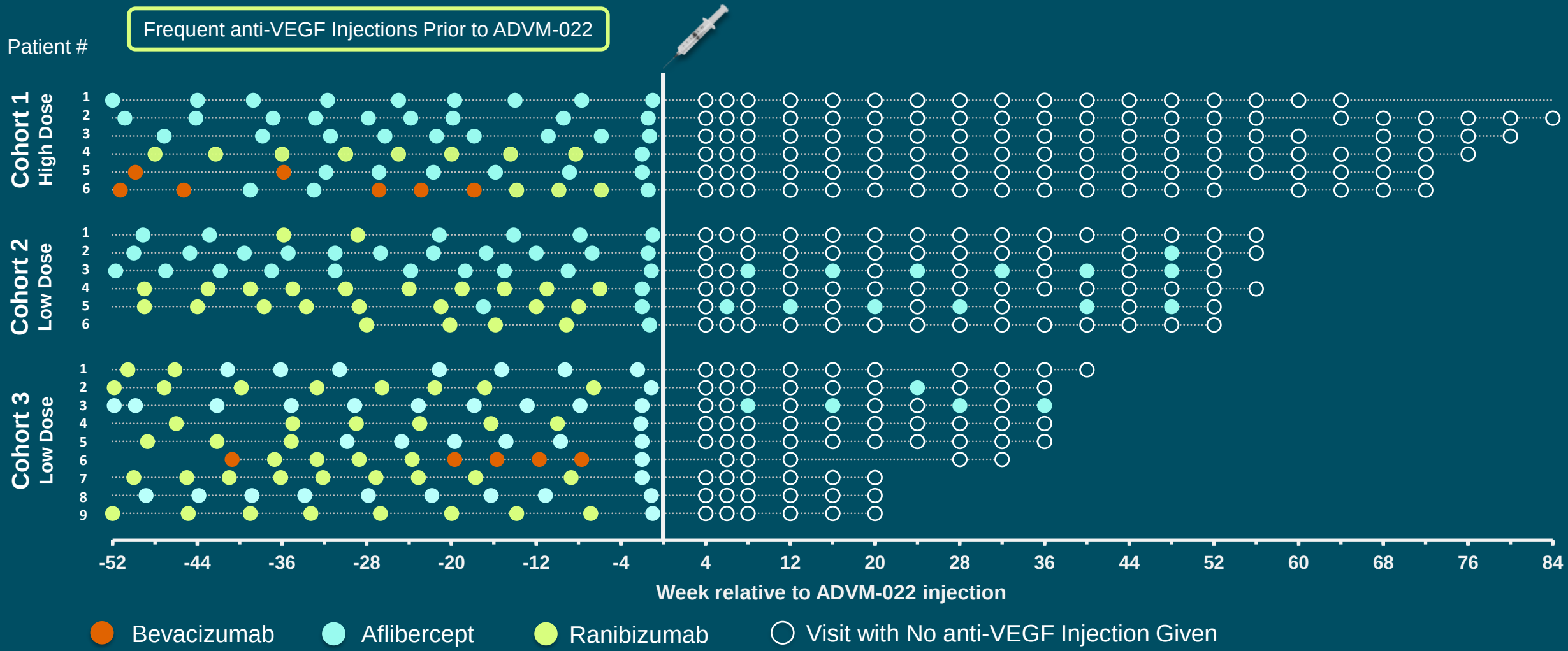



+36 weeks
BCVA: 83 letters
CST: 286 µm

BCVA, best-corrected visual acuity; CST, central subfield thickness; IVT, intravitreal injection

Substantial Reduction in anti-VEGF Treatments Following a Single IVT Injection of ADVM-022

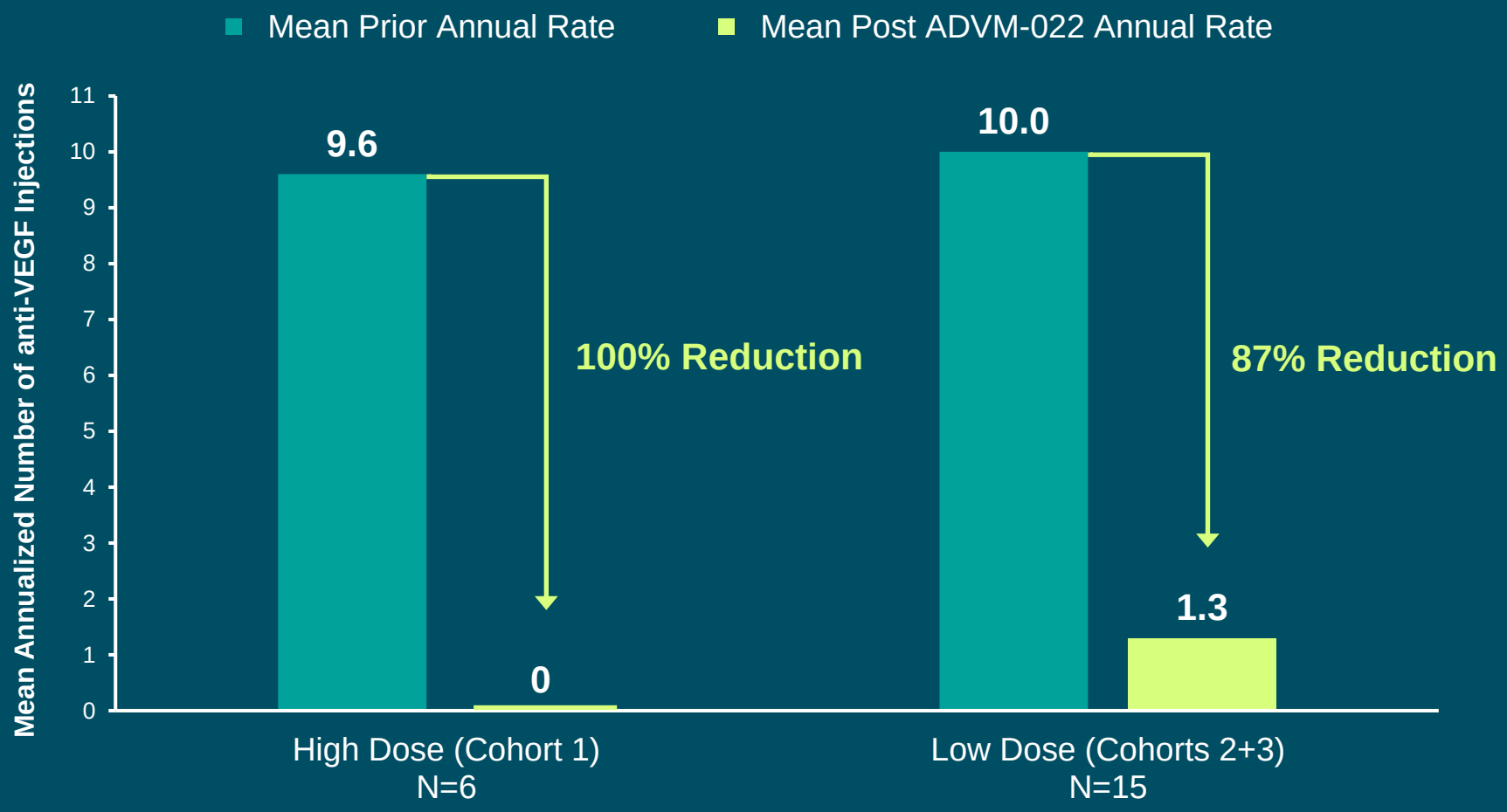


Two patients (Cohort 1 subject 1 and Cohort 3 subject 6) missed two or more consecutive visits due to COVID-19 concerns

VEGF, vascular endothelial growth factor; IVT, Intravitreal

Data cut: July 23, 2020

Substantial Reduction in Annualized anti-VEGF Injection Frequency Following ADVM-022



Annualized rate (Prior) = (number of IVTs in 12 months prior to ADVM-022) / (days from the first IVT in the past 12 months to ADVM-022 / 365.25).

Annualized rate (Post) = (number of aflibercept IVTs since ADVM-022) / (days from ADVM-022 to the last study follow-up / 365.25).

Data cut: July 23, 2020

ADVM-022 Demonstrates Further Potential to Greatly Reduce Treatment Burden in wet AMD

- ADVM-022 continues to show robust treatment response
  - Mean BCVA maintained
  - Mean CST maintained to improved
- Long-term durability beyond 15 months from single IVT injection with zero rescue injections in Cohort 1
- Further evidence of a dose response:
  - High dose: 6/6 patients rescue injection free
  - Low dose: 10/15 patients rescue injection free
- Substantial reduction in annualized anti-VEGF injection frequency following ADVM-022:
  - High dose: 100%
  - Low dose: 87%
- ADVM-022 continues to be well tolerated with a favorable safety profile in all 4 cohorts (n=30)
  - All ADVM-022-related ocular adverse events were mild (78%) to moderate (22%)
  - Ocular inflammation, when observed, has been responsive to steroid eye drops
- ADVM-022 warrants further investigation in larger studies

AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; CST, central subfield thickness; VEGF, vascular endothelial growth factor; IVT, intravitreal

Data cut: July 23, 2020

ADVM-022 Acknowledgments

Investigators, Study Teams and Participants

- David Boyer MD
- Brandon Busbee MD
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- James Major MD
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- Charles Wykoff MD, PhD
- Mehdi Gasmi PhD
- Szilard Kiss MD
- Aaron Osborne MBBS
- Carol Hoang PharmD
- Adam Turpcu PhD
- Carol Chung PhD

INFINITY: Phase 2 Trial of ADVM-022 in DME

Multi-center, randomized, double-masked, active comparator-controlled

INFINITY Gene Therapy in DME

- Evaluate a single IVT injection of ADVM-022 in patients with vision impairment due to center involving diabetic macular edema (DME)
- Designed to demonstrate superior disease control compared to a single aflibercept injection, measured by time to worsening of DME disease activity
- Additional objectives assess frequency of rescue aflibercept to the study eye, visual acuity (BCVA), retinal anatomy (OCT and DRSS) and safety outcomes

Day 1: Aflibercept/Sham

Day 8: ADVM-022/Sham

Patients receive rescue aflibercept (2 mg IVT) if **either** of the following disease activity criteria are met:

1. Loss of >5 letters in BCVA from best prior BCVA, due to worsening DME disease activity
2. Increase in central subfield thickness (CST) >50 µm from best prior CST

Screening and Randomization

Clinical assessments with rescue aflibercept from week 8

Weeks: 4 8 12 16 20 24 PE** 28 32 36 40 44 48 EOS***

Steroid eye drops prophylaxis*

Recent onset DME

R

Arm 1: ADVM-022 $6x10^{11}$ vg IVT

Arm 2: ADVM-022 $2x10^{11}$ vg IVT

Arm 3: Aflibercept 2 mg IVT

DRSS, Diabetic Retinopathy Severity Score
OCT, Optical Coherence Tomography
CST, Central Subfield Thickness

*All subjects receive a 7-week course of difluprednate eye drops, starting at QID and tapering to QD
**PE= Primary Endpoint assessment
***EOS= End of Study assessment

www.INFINITYclinicaltrial.com or
https://www.clinicaltrials.gov/ct2/show/NCT04418427

Thank you


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BIOTECHNOLOGIES