# Intravitreal Gene Therapy for Diabetic Macular Edema with ADVM-022: First-Time Data Presentation of Prospective, Randomized Phase 2 INFINITY Trial

Charles C Wykoff, MD, PhD

on behalf of the INFINITY investigators

# CCW Disclosures

- *Adverum: Member of Scientific Advisory Board*
- *Consultant:* Aerie Pharmaceuticals, Allergan, Allgenesis, Apellis, Arrowhead Pharmaceuticals, Bausch + Lomb, Bayer, Bionic Vision Technologies, Chengdu Kanghong Biotechnologies (KHB), Clearside Biomedical, EyePoint Pharmaceuticals, Genentech, Gyroscope, IVERIC Bio, Janssen, Kato Pharmaceuticals, Kodiak Sciences, Long Bridge Medical, NGM Biopharmaceuticals, Novartis, OccuRx, Ocular Therapeutix, ONL Therapeutics, Opthea Limited, Oxurion, Palatin, PolyPhotonix, RecensMedical, Regeneron, RegenXBio, Roche, Surrozen, Takeda, Verana Health, Vitranu
- *Research:* Adverum, Aerie Pharmaceuticals, Aldeyra, Alimera Sciences, Allergan, Amgen, Apellis, Asclepix, Bayer, Boehringer Ingelheim, Chengdu Kanghong Biotechnology, Clearside Biomedical, Gemini, Genentech, Graybug Vision, Gyroscope, IONIS Pharmaceutical, iRENIX, IVERIC bio, Kodiak Sciences, LMRI, Neurotech Pharmaceuticals, NGM Biopharmaceuticals, Novartis, Oxurion, RecensMedical, Regeneron, RegenXBio, Roche, SamChunDang Pharm, Taiwan Liposome Company, Xbrane BioPharma
- *Ownership/Stock:* ONL Therapeutics, PolyPhotonix, RecensMedical, Visgenx

# ADVM-022 is a Novel Biofactory Approach to Gene Therapy

*Designed for continuous delivery of aflibercept following intravitreal injection*

**AAV.7m8 capsid**

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

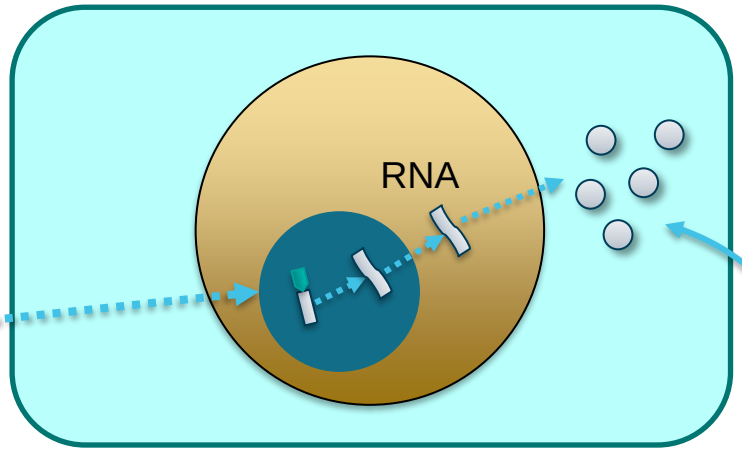
Promoter

Aflibercept

Aflibercept Expression Cassette

Strong, Ubiquitous Promoter Designed for Robust Protein Expression

In a preclinical study, aflibercept protein levels reached therapeutic levels 3 months post injection




Target Retinal Cell Expresses Aflibercept

Codon-Optimized cDNA

IVT, intravitreal

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

# INFINITY DME Study Key Takeaways

**STUDY UNMASKING (MAY 4, 2021): Unexpected SAE of hypotony and IOI**

- A dose-limiting toxicity (DLT) with ADVM-022 at $6X10^{11}$ vg/eye was reported in a DME patient with severe comorbidities
  - Initial patient and 2 additional cases reported after data cut required surgery
- Adverum immediately unmasked INFINITY to identify and manage patient safety
- Subsequent patients stabilized with aggressive steroid management and immunosuppressive therapy

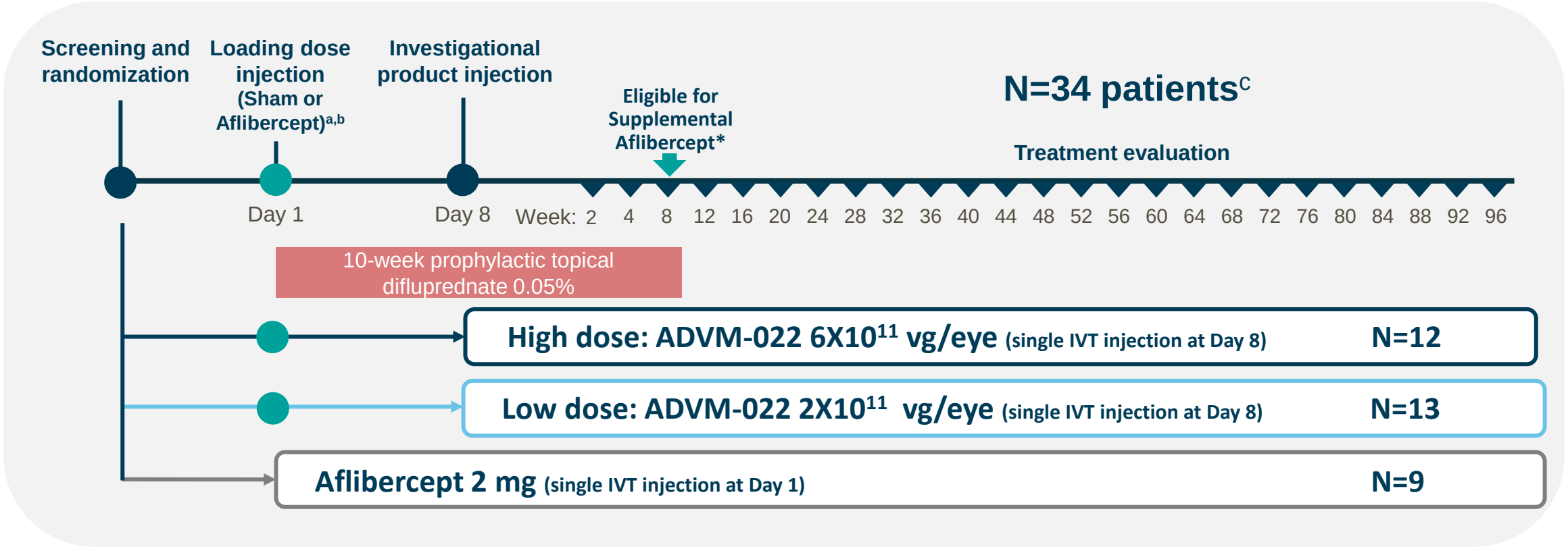
## Key learnings from the INFINITY study:

**Disease state & ADVM-022 dose appear to have an impact in determining the therapeutic window which balances efficacy and safety:**

- Dose-dependent inflammation observed in DME patients with dose-limiting toxicity at $6x10^{11}$ vg/eye may be in part related to the comorbid nature of the study population
- No clinically relevant reduction in IOP was observed in the ADVM-022 $2x10^{11}$ vg/eye group

https://www.globenewswire.com/news-release/2021/07/22/2267699/32452/en/Adverum-Provides-Update-on-ADVM-022-and-the-INFINITY-Trial-in-Patients-with-Diabetic-Macular-Edema.html

# INFINITY Phase 2 Study Design




- **Objective:** Assess the durability, safety and efficacy of a single IVT injection of ADVM-022 in patients with DME
- **Primary Endpoint:** Time to worsening of DME disease activity in the study eye (first supplemental aflibercept injection)

***Supplemental aflibercept criteria (2 mg IVT):**

Eligible starting week 8, with minimum 21 days between supplemental injections if meeting the conditions below:

- CST>50µm (relative to day 1 and week 4)
- Loss of >5 BCVA letters compared with the higher of two measurements recorded on day 1 or week 4

AFL, aflibercept; BCVA, best corrected visual acuity; CST, central subfield thickness; DME, diabetic macular edema; IVT, intravitreal.
[a]Aflibercept/Sham was dosed on day 1. Subsequently aflibercept injections based on supplemental aflibercept criteria starting at Week 8.
[b]Aflibercept arm received aflibercept at Day 1. [c]36 patients randomized.
https://www.clinicaltrials.gov/ct2/show/NCT04418427

**Data cut off: June 22, 2021; All data unmasked: May 4, 2021**

# Baseline Characteristics in INFINITY

| | ADVM-022 6X10$^{11}$ (N=12) | ADVM-022 2X10$^{11}$ (N=13) | Aflibercept (N=9) |
|---|---|---|---|
| **Mean (range) Age, Years** | 63 (55 - 74) | 60 (46 - 77) | 57 (47 - 64) |
| **Male Gender, n (%)** | 7 (58) | 9 (69) | 4 (44) |
| **Race** | | | |
| White, n (%) | 10 (83) | 10 (77) | 9 (100) |
| Black, n (%) | 1 (8) | 3 (23) | 0 (0) |
| Other, n (%) | 1 (8) | 0 (0) | 0 (0) |
| **Ethnicity (% Hispanic or Latino)** | 7 (58) | 7 (54) | 6 (67) |
| **Diabetes Status** | | | |
| Mean A1C (range) | 8.1 (6.2 - 9.8) | 7.0 (5.7 - 9.1) | 7.6 (5.9 - 9.1) |
| Type 2 Diabetes, % | 100 | 100 | 100 |
| Diabetes Disease Duration, years (range) | 13.4 (0.3 - 30.8) | 18.2 (0.9 - 33.9) | 13.5 (0.9 - 29.5) |
| **Vascular Status[a]** | | | |
| Abnormal, n (%) | 11 (92) | 12 (92) | 8 (89) |
| **Renal Status[b]** | | | |
| Abnormal, n (%) | 2 (17) | 1 (8) | 0 (0) |

[a]Vascular status includes cardiac disease and peripheral vascular disease;
[b]Renal status includes chronic kidney disease and stage 2 and 3 kidney diseases.
Aflibercept/Sham was dosed on day 1. Subsequently aflibercept injections based on supplemental aflibercept criteria starting at Week 8.

**Data cut off: June 22, 2021; All data unmasked: May 4, 2021**

# Baseline Ocular Characteristics in INFINITY

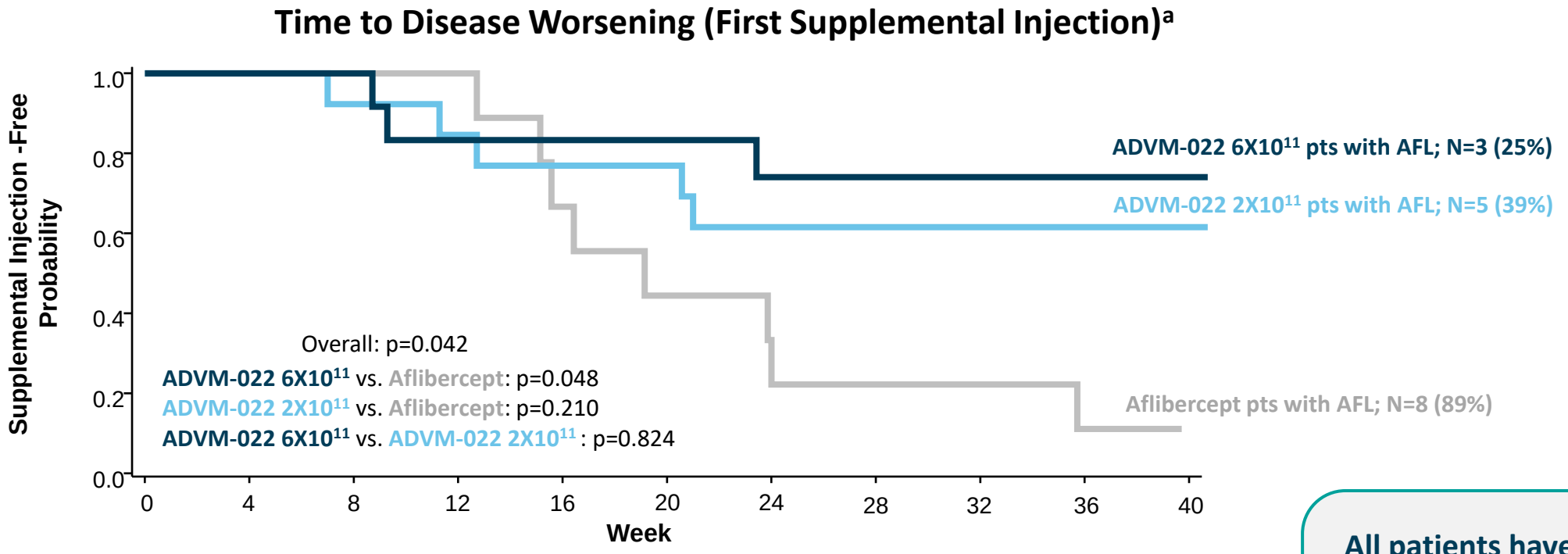
| | ADVM-022 6X10$^{11}$ (N=12) | ADVM-022 2X10$^{11}$ (N=13) | Aflibercept (N=9) |
|---|---|---|---|
| **BCVA, mean (range), EDTRS Letter** | 64 (47 - 78) | 68 (50 - 82) | 61 (40 – 75) |
| **CST, mean (range), µm** | 485 (302 – 746) | 443 (311 – 681) | 472 (328 – 668) |
| **IOP, mean (range), mmHg** | 16.0 (12 - 19) | 16.8 (12 - 24) | 15.9 (8 - 21) |
| **Phakic, %** | 83.3 | 84.6 | 88.9 |
| **Anti-VEGF Treatment Naïve, %** | 92 | 92 | 89 |
| **Bilateral DME, %** | 75 | 69 | 100 |
| **DRSS** | | | |
| Mild NPDR (DRSS ≤ 35), n(%) | 4 (33) | 5 (38) | 4 (44) |
| Moderate NPDR (DRSS = 43), n(%) | 2 (17) | 1 (8) | 1 (11) |
| Moderately Severe to Severe NPDR (DRSS 47 - 53), n(%) | 4 (33) | 5 (38) | 4 (44) |
| Mild to Moderate PDR (DRSS 61 - 65), n(%) | 2 (17) | 2 (15) | 0 (0) |

BCVA, best corrected visual acuity; CST, central subfield thickness; DME, diabetic macular edema; DRSS, diabetic retinopathy severity scale; IOP, intraocular pressure; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; VEGF, vascular endothelial growth factor. Aflibercept/Sham was dosed on day 1. Subsequently aflibercept injections based on supplemental aflibercept criteria starting at Week 8.

**Data cut off: June 22, 2021; All data unmasked: May 4, 2021**

# Week 24 Primary Endpoint – Time to worsening of DME disease activity

## Kaplan Meier Curve: Proportion of Patients Supplemental Aflibercept Injection Free Over Time




**Number who Reached Visit (Number At-Risk)**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ADVM-022 6X10$^{11}$ | 12 (12) | 12 (12) | 12 (12) | 12 (10) | 12 (10) | 12 (10) | 12 (7) | 9 (5) | 7 (5) | 4 (4) | 3 (3) |
| ADVM-022 2X10$^{11}$ | 13 (13) | 13 (13) | 13 (12) | 13 (11) | 13 (10) | 13 (10) | 11 (7) | 7 (5) | 6 (3) | 4 (3) | 3 (1) |
| Aflibercept | 9 (9) | 9 (9) | 9 (9) | 9 (9) | 9 (6) | 9 (4) | 9 (3) | 6 (2) | 4 (2) | 4 (1) | 2 (0) |

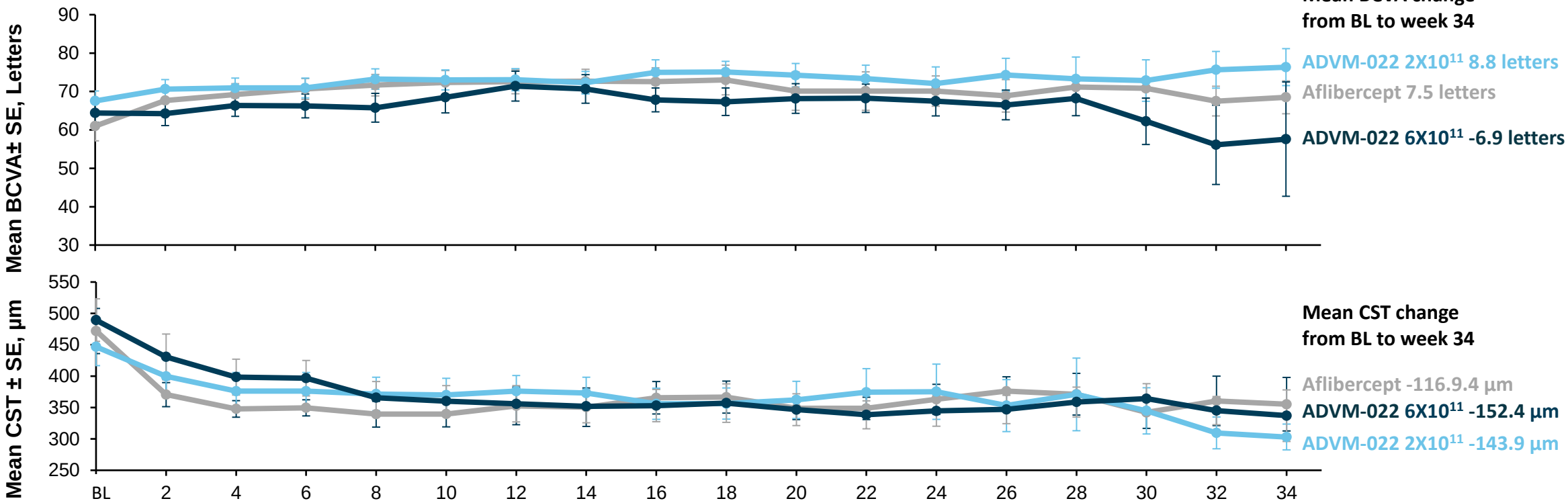
**All patients have completed through ≥ Week 24**

**Median Follow-up approximately 30 weeks**

AFL, aflibercept; BCVA, best corrected visual acuity; CST, central subfield thickness; DME, diabetic macular edema; Pts, patients.
[a]Supplemental aflibercept criteria (2 mg IVT): (1) Not eligible for supplemental aflibercept until week 8 (minimum 21 days between injections); (2) CST>50µm (relative to day 1 and week 4); (3) Loss of >5 BCVA letters compared with the higher of two measurements recorded on day 1 or week 4.
Patients with inflammation in the ADVM groups resulted in excessive steroid use, which confounds the interpretation of efficacy results.
Aflibercept/Sham was dosed on day 1. Subsequently aflibercept injections based on supplemental aflibercept criteria starting at Week 8.

**Data cut off: June 22, 2021; All data unmasked: May 4, 2021**

# BCVA and CST in INFINITY over 34 Weeks[a]




| Sample size: | BL | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 30 | 32 | 34 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ADVM-022 6X10$^{11}$ | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 10 | 9 | 8 | 7 | 4 |
| ADVM-022 2X10$^{11}$ | 13 | 13 | 13 | 13 | 13 | 13 | 13 | 13 | 13 | 13 | 13 | 12 | 11 | 10 | 7 | 7 | 6 | 6 |
| Aflibercept | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 6 | 6 | 4 | 4 |

BCVA, best corrected visual acuity; BL, baseline; CST, central subfield thickness; DME, diabetic macular edema.
[a]Data were cut to week 34 because the sample size was <4.
Inflammation patients treated with ADVM resulted in excessive steroid use, which confounds the interpretation of efficacy results.
Aflibercept/Sham was dosed on day 1. Subsequently aflibercept injections based on supplemental aflibercept criteria starting at Week 8.

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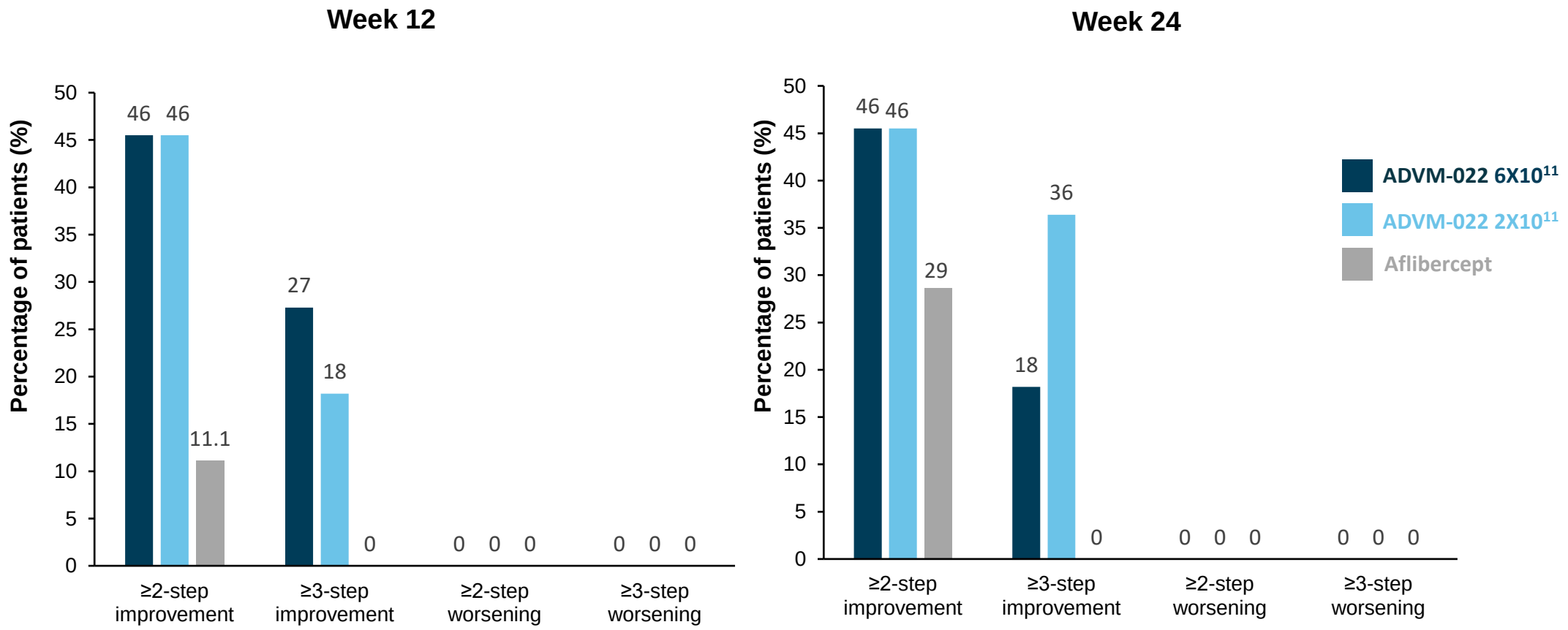
# Improvement in DRSS in DME Patients Treated with ADVM-022




DME, diabetic macular edema; DRSS, diabetic retinopathy severity scale.
Aflibercept/Sham was dosed on day 1. Subsequently aflibercept injections based on supplemental aflibercept criteria starting at Week 8.

**Data cut off: June 22, 2021; All data unmasked: May 4, 2021**

# The Proportion of DME Patients with Non-Ocular Adverse Events Were Similar Between all Cohorts

| Non-Ocular AEs | ADVM-022 6X10$^{11}$ (N=12) | | ADVM-022 2X10$^{11}$ (N=13) | | Aflibercept (N=9) | |
|---|---|---|---|---|---|---|
| | Subjects (%) | Events | Subjects (%) | Events | Subjects (%) | Events |
| AEs | 7 (58) | 18 | 6 (46) | 31 | 6 (67) | 16 |
| SAE | 1 (8) | 3 | 3 (23) | 6 | 0 (0) | 0 |
| Renal | 1 (8) | 1 | 1 (7) | 3 | 0 (0) | 0 |
| Non-Renal | 1(8) | 2 | 2 (15) | 3 | 0 (0) | 0 |
| IP-Related[a], n(%) | 0 (0) | 0 | 0 (0) | 0 | 0 (0) | 0 |

AE, adverse event; DME, diabetic macular edema; IP, investigational product; SAE, severe adverse event.
n (%) of participants with event reported in each dose group reported
[a]Related events are any that are assessed as likely or definitely related to investigational product (IP).
Aflibercept/Sham was dosed on day 1. Subsequently aflibercept injections based on supplemental aflibercept criteria starting at Week 8.

**Data cut off: June 22, 2021; All data unmasked: May 4, 2021**

# More DME Patients in the ADVM-022 Cohorts Experienced IOI Compared to the Aflibercept Cohort

| | ADVM-022 6X10$^{11}$ (N=12) | | ADVM-022 2X10$^{11}$ (N=13) | | Aflibercept (N=9) | |
|---|---|---|---|---|---|---|
| | Subjects (%) | Events | Subjects (%) | Events | Subjects (%) | Events |
| **Ocular SAE[a]** | **2 (17)** | **3** | **0 (0)** | **0** | **1 (11)** | **1** |
| **Any IOI** | **10 (83)** | **20** | **12 (92)** | **20** | **3 (33)** | **3** |
| Any Anterior IOI | 9 (75) | 18 | 11 (85) | 19 | 3 (33) | 3 |
| Any Posterior IOI | 2 (17) | 2 | 1 (8) | 1 | 0 (0) | 0 |
| Vasculitis / Endophthalmitis | 0 (0) | 0 | 0 (0) | 0 | 0 (0) | 0 |
| **Any Iris-Related Event** | **8 (67)** | **16** | **7 (54)** | **17** | **0 (0)** | **0** |
| Transillumination Defects (any severity) | 6 (50) | 6 | 4 (31) | 4 | 0 (0) | 0 |
| Synechiae | 5 (42) | 5 | 4 (31) | 4 | 0 (0) | 0 |
| Pigmentary Changes (Anterior) | 5 (42) | 5 | 6 (46) | 9 | 0 (0) | 0 |
| **Hypotony** | **3 (25)** | **3*** | **0 (0)** | **0** | **0 (0)** | **0** |

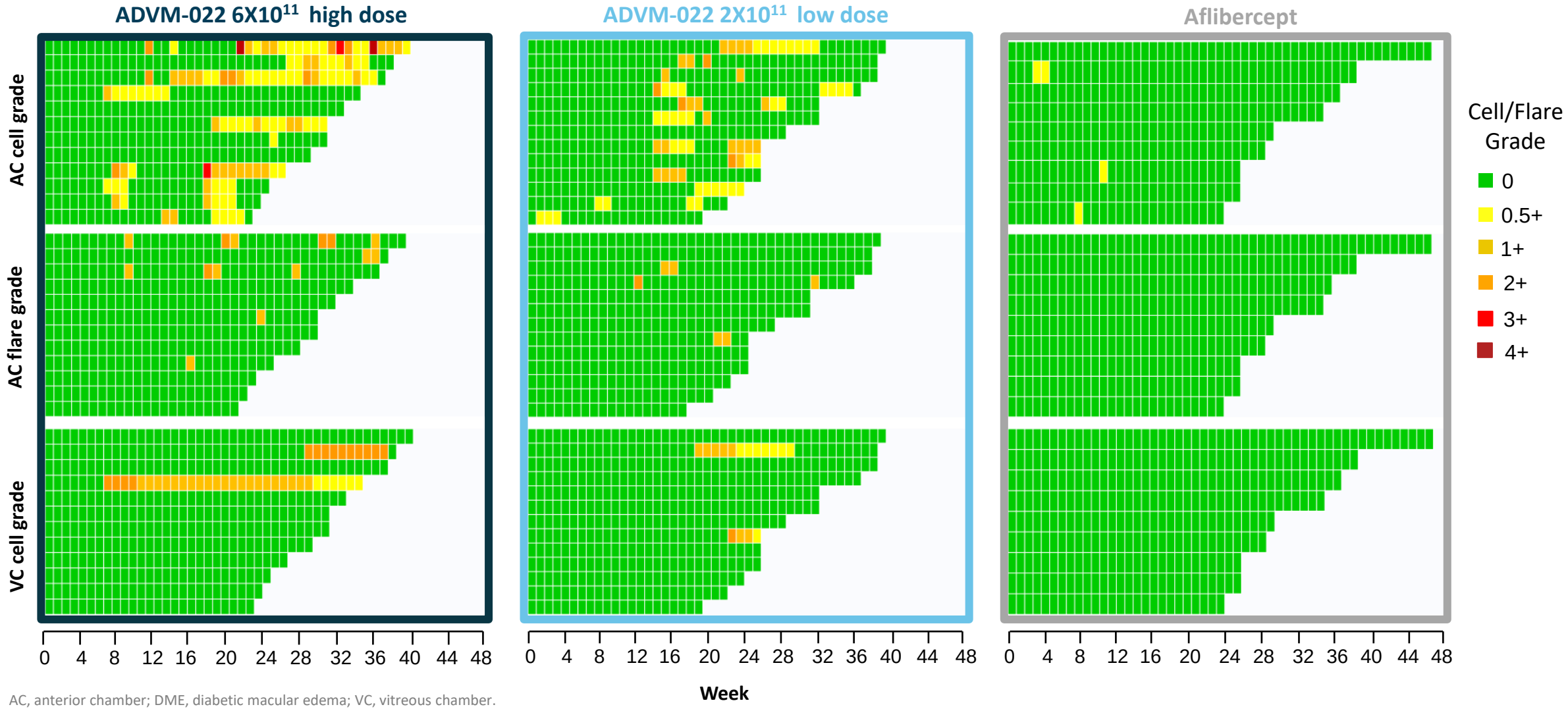
ADVM-022-related AEs were 57% mild, 41% moderate, and 2% severe

*Two additional cases of hypotony occurred at 6x10$^{11}$ vg/eye after the data cut off

DME, diabetic macular edema; IOI, intraocular inflammation; SAE, severe adverse event.
[a]3 Ocular SAEs for 6E11: Hypotony, Worsening of Anterior Uveitis, Increase in Cells; 1 Ocular SAE for Aflibercept: Worsening Cataract. n (%) of participants with event reported in each dose group reported.
Aflibercept/Sham was dosed on day 1. Subsequent aflibercept injections based on supplemental aflibercept criteria starting at Week 8.
Five Total Cases of Hypotony. Three occurred prior to the data cutoff. Two occurred after the data cutoff. Three required surgery.

**Data cut off: June 22, 2021; All data unmasked: May 4, 2021**

# Dose-Dependent Inflammation Observed in DME Patients Over Time



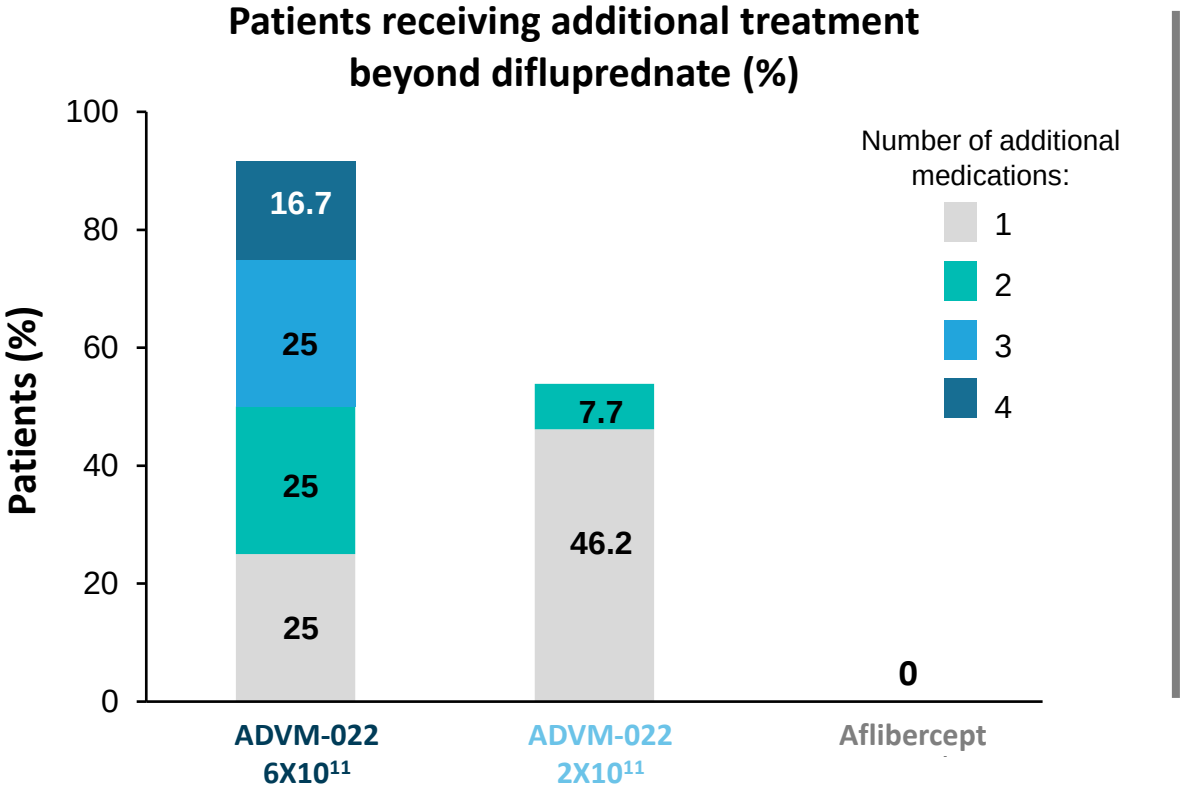

AC, anterior chamber; DME, diabetic macular edema; VC, vitreous chamber.
AC: 0.5+: 1-5 cells 1+: 6-15 cells 2+: 16-25 cells 3+: 26-50 cells 4+: >50 cells
VC: 0.5+: 1-10 cells 1+: 11-20 cells 2+: 21-30 cells 3+: 31-100 cells 4+: >100 cells; Rare cells are captured as 0.5+ for this analysis
Cell grades as assessed by slit lamp; Grade categories are based on the Standardization of Uveitis Nomenclature (SUN) criteria for aqueous cells and National Institutes of Health (NIH) guidelines for vitreous cells.
Aflibercept/Sham was dosed on day 1. Subsequently aflibercept injections based on supplemental aflibercept criteria starting at Week 8.

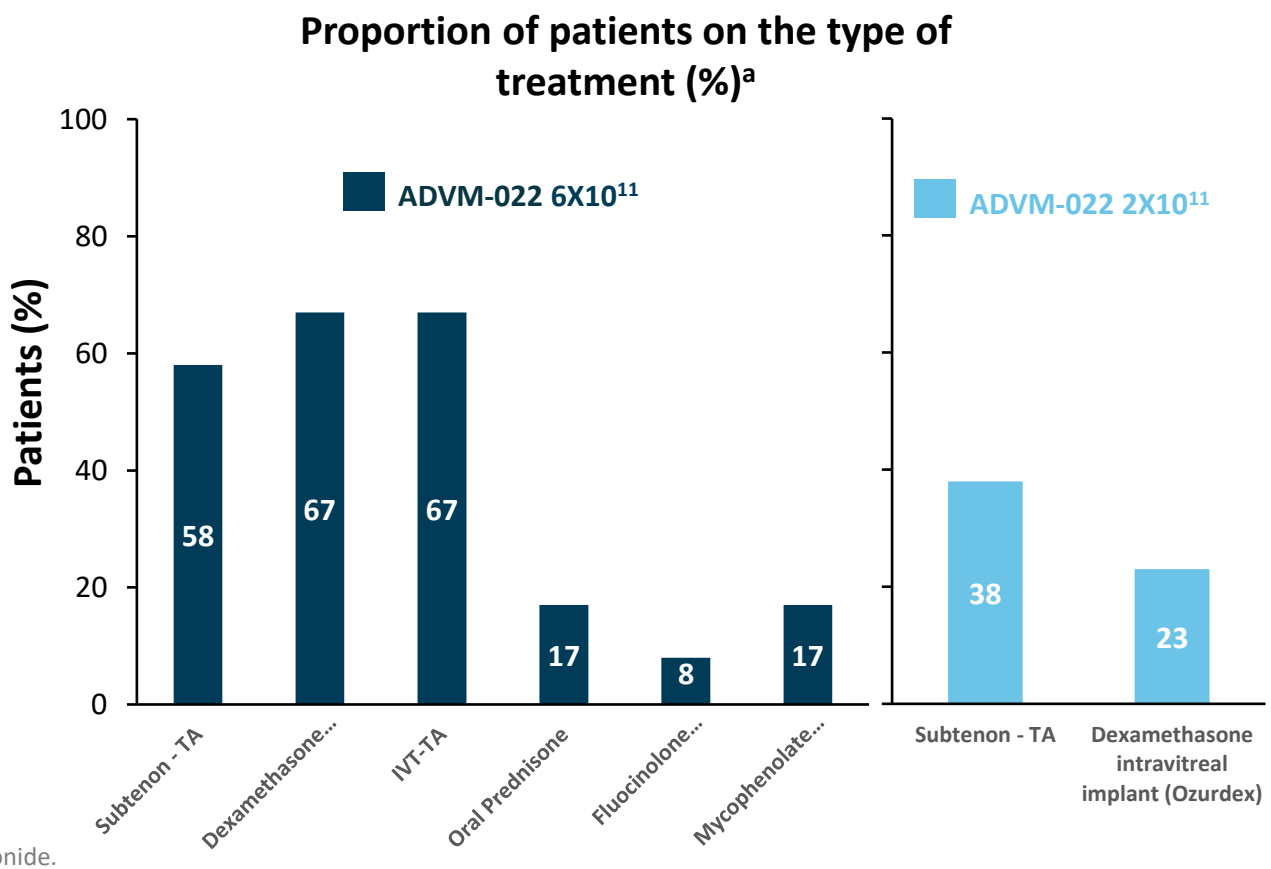
**Data cut off: June 22, 2021; All data unmasked: May 4, 2021**

# DME Patients Received Additional Treatment Beyond Prophylaxis

100% of patients in the ADVM-022 6X10$^{11}$ group, 92% in the ADVM-022 2X10$^{11}$ group, and 44% in the aflibercept group received additional difluprednate (Durezol) beyond the prophylaxis period of 10 weeks

**After study unmasking, patients were aggressively treated for any sign of potential low IOP or inflammation**




DME, diabetic macular edema; IOP, intraocular inflammation; IVT, intravitreal; TA, triamcinolone acetonide.
[a]Patients may have received more than one type of treatment.
Aflibercept/Sham was dosed on day 1. Subsequently aflibercept injections based on supplemental aflibercept criteria starting at Week 8.

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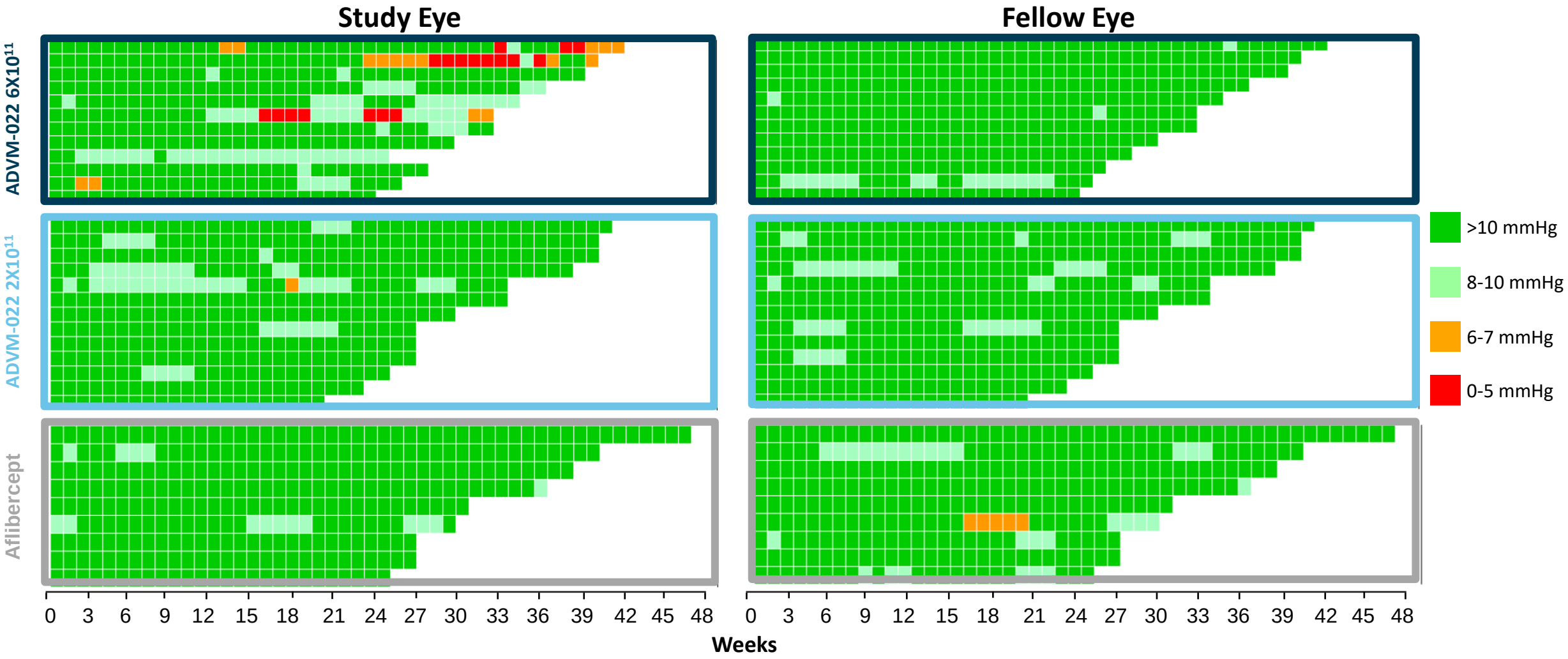
# Unexpected AE of Hypotony at ADVM-022 6x10$^{11}$ Dose in DME

## Dose-Dependent Changes in IOP Over Time




**Three patients in the ADVM-022 6x10$^{11}$ arm underwent surgery at week 35 (n=1) and 37 (n=2)**

AE, adverse event; DME, diabetic macular edema; IOP, intraocular pressure

Aflibercept/Sham was dosed on day 1. Subsequently aflibercept injections based on supplemental aflibercept criteria starting at Week 8.

**Data cut off: June 22, 2021; All data unmasked: May 4, 2021**

# Three Hypotony Patients Have Required Surgical Intervention
# All Three Were Treated with 6x10$^{11}$ vg/eye

**Patient 1**
**Aflibercept+ ADVM-022 6X10$^{11}$**

Hx: CAD, 2MIs, stents, 2 blood clots (left leg), peripheral edema, diabetic neuropathy
**DRSS = 47; BL Cr = 1.2**

**Renal Failure** — **Initial IOI** — **Hypotony[b]** — **Surgery** (Vitrectomy, Oil, Retisert)

**Patient 2[a]**
**Aflibercept+ ADVM-022 6X10$^{11}$**

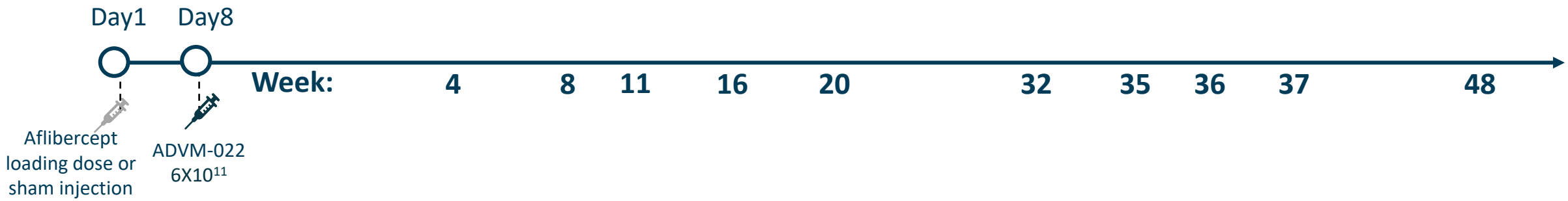
Hx: Hypertension, hyperlipidemia, neuropathy, diabetic foot ulcer
**DRSS = 47; BL Cr = 0.8**

**Hypotony[b]** — **Surgery** (Vitrectomy, Oil, Retisert)
**Initial IOI**

**Patient 3[a]**
**Sham+ ADVM-022 6X10$^{11}$**

Hx: Aneurysm, peripheral neuropathy, diabetic foot ulcer, acute respiratory failure, renal failure
**DRSS = 47; BL Cr = 2.0**

**Renal Failure** — **Initial IOI** — **Hypotony[b]** — **Surgery** (Vitrectomy, Oil, Retisert)

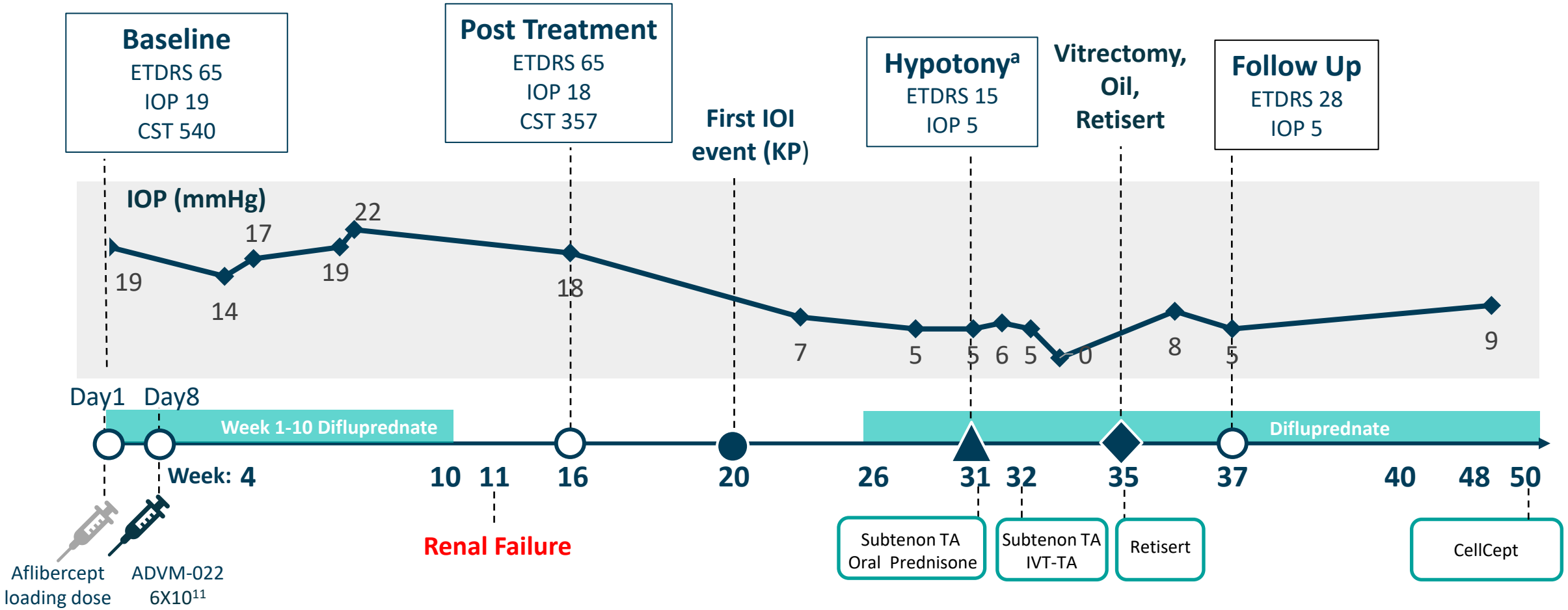



BL, baseline; CAD, coronary artery disease; Cr, creatinine; DME, diabetic macular edema; DRSS, diabetic retinopathy severity scale; MI, myocardial infarction
[a]Hypotony and surgeries in patients 2 and 3 occurred after data cut off; [b]Hypotony defined as Intraocular pressure (IOP) ≤5 mm Hg
Aflibercept/Sham was dosed on day 1. Subsequently aflibercept injections based on supplemental aflibercept criteria starting at Week 8.

**Data cut off: June 22, 2021; All data unmasked: May 4, 2021**

# Case Example: Hypotony with Serous Choroidals and Panuveitis 31 weeks after ADVM-022 6x10$^{11}$ vg/eye

**56-year-old American Indian female with Type 2 DM for 4 years (2017), A1C of 9.1%**
**Medical History: CAD, 2 MIs, stents, 2 blood clots (left leg), peripheral edema, diabetic neuropathy. DRSS=47**




CAD, coronary artery disease; CST, central subfield thickness; DM2, diabetes mellitus type 2; DME, diabetic macular edema; DRSS, diabetic retinopathy severity scale; IOI, intraocular inflammation; IOP, intraocular pressure; KP, keratic precipitate; MI, myocardial infarction; TA, triamcinolone acetonide.

[a] Hypotony defined as Intraocular pressure (IOP) ≤5 mm Hg

**Data cut off: June 22, 2021; All data unmasked: May 4, 2021**

# Mechanisms Underlying Hypotony at $6x10^{11}$ vg/eye in DME Are Unknown
## *Hypotheses Under Investigation*

### Study Population Context

- In diabetes, microvascular and macrovascular disease may impair ciliary body function[2-4] potentially leading to hypoperfusion / vascular insufficiency with additional insults
- Breakdown of the blood-aqueous barrier and blood-retina-barrier in long-term diabetics contributes to ciliary body impairment and exposure to the immune system[5,6]

### Dose Factors

- At high doses, the immune response to gene therapy may be both local and systemic, requiring more intensive prophylactic regimens[1]

### Potential Ciliary Body Impact of ADVM-022 at $6x10^{11}$ vg/eye in Eyes with DME

- A toxic effect or immune response to gene therapy
- A local anti-VEGF effect
- A combination of these and other events

CB, ciliary body; CVD, cardiovascular disease

1. Bucher et al. *Prog Retin Eye Res* 2021;83:100915. 2. Kiel JW et al, *Prog Retin Eye Res.* 2011;30(1):1-17. 3. Flemmer J et al, *Eur Heart J.* 2013; 34: 1270–1278. 4.Hayashi M et al, *Br J Ophthalmol*. 1989;73:621-623. 5. Mesquida et al. *Semin Immunopathol.* 2019;41(4):427-445. 6. Katamay and Nussenblatt. *Retina.* 2013: 579-589.

# Additional efforts deployed to ensure patient safety and better understand the DLT observed in DME patients at $6x10^{11}$ vg/eye

**A comprehensive approach including Preclinical, CMC, Clinical, and Expert Advisors (including leading retina, uveitis, glaucoma, and imaging experts)**


- **Real-time monitoring**
  - Regular site reviews & PI-to-PI information sessions
- **Increased DMC meetings**
- **Uveitis Specialist added as medical monitor**
- **Active patient management, tracking and adjusting response to treatment**
- **Regular review of clinical cases**

- **Slit Lamp Cameras and Ultrasound Biomicroscopy** to better capture and describe inflammation and hypotony
- **Enhanced anterior and posterior imaging analysis** is being conducted in partnership with Cleveland Clinic

- **Aqueous Testing: Metagenomic deep sequencing, Protein expression, Cytokine profiling, Cytology**
- **Serum Testing: TAbs, NAbs, anti-drug antibodies, ELISPOT**

# Conclusions From the Interim Analysis of the INFINITY Study

**ADVM-022 dose & disease state appear to have an impact in determining the therapeutic window which balances efficacy and safety:**

- Dose-dependent inflammation observed in DME patients with dose-limiting toxicity at $6x10^{11}$ vg/eye may be in part related to the comorbid nature of the study population
- No clinically relevant reduction in IOP was observed in the ADVM-022 $2x10^{11}$ vg/eye group

**Outstanding research questions:**

- The difference in safety profiles between the OPTIC and INFINITY studies highlight the need to consider the severe comorbid nature of patients with DME (including renal failure):
  - Microvascular and macrovascular disease lead to breakdown of the blood-aqueous and blood-retina-barriers, leading to baseline ciliary body dysfunction in DME patients[1-4]
- Dose-dependent gene therapy-associated inflammation has been reported previously and a better understanding of causes and optimal prophylactic management will be studied further

- ADVM-022 development plan will focus on nAMD and low doses ($2x10^{11}$ vg/eye and lower)

*1.* Kiel JW et al, *Prog Retin Eye Res.* 2011;30(1):1-17. 2. Flemmer J et al, *Eur Heart J.* 2013; 34: 1270–1278. 3.Hayashi M et al, *Br J Ophthalmol*. 1989;73:621-623. 4. Katamay and Nussenblatt. *Retina.* 2013: 579-589.

# Thank You

- Sites
- Investigators
- Patients
- Site staff