ADVM-022 Intravitreal Gene Therapy for Neovascular AMD: OPTIC Phase 1 Study Update

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OPTIC
Gene Therapy in nAMD

Disclosures

- **Consultant/Advisory**: Genentech, Regeneron, RegenXBio, **Adverum**, Gemini, NGM, IVERIC, Unity, Ophthea, Clearside

- **Research Funding**: Genentech, Regeneron, RegenXBio, **Adverum**, Gemini, NGM, Stealth, Unity, Apellis, Novartis, Kodiac, Chengdu Kanghong, IVERIC, Ocular Therapeutix, 4D-MT, Valo, Ophthea, Oxurion, Greybug, Clearside, Annexon, Alimera

OPTIC Study: Designed to Evaluate the Safety and Efficacy of ADVM-022 for nAMD

Status

- 4 cohorts fully enrolled
- Follow-up to 104 weeks

Primary Objective

- Assess the safety and tolerability of a single IVT injection of ADVM-022

Secondary Objectives

- Evaluate vision maintenance (BCVA)
- Evaluate anatomy (SD-OCT)
- Assess the need for supplemental therapy
- Evaluate effect of ADVM-022 on presence of IRF & SRF

	Prophylaxis Steroid Regimen
Cohort 1 (n=6) 6 x 10^{11} high dose	Oral*, 13d
Cohort 2 (n=6) 2 x 10^{11} low dose	Oral*, 13d
Cohort 3 (n=9) 2 x 10^{11} low dose	Eye Drops**, 6 wks
Cohort 4 (n=9) 6 x 10^{11} high dose	Eye Drops**, 6 wks

Supplemental Aflibercept (2 mg IVT) Criteria:

1. Loss of ≥10 letters in BCVA (ETDRS) 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 received prophylaxis of QID difluprednate eye drops for 3 weeks starting at Day 1 followed by a 3-week taper.*
AAV, adeno-associated virus; AMD, age-related macular degeneration; BCVA, best corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; IVT, intravitreal therapy; NAb, neutralizing antibody; QID, four times daily; SD-OCT, spectral domain optical coherence tomography; NCT03748784.

Safety Summary

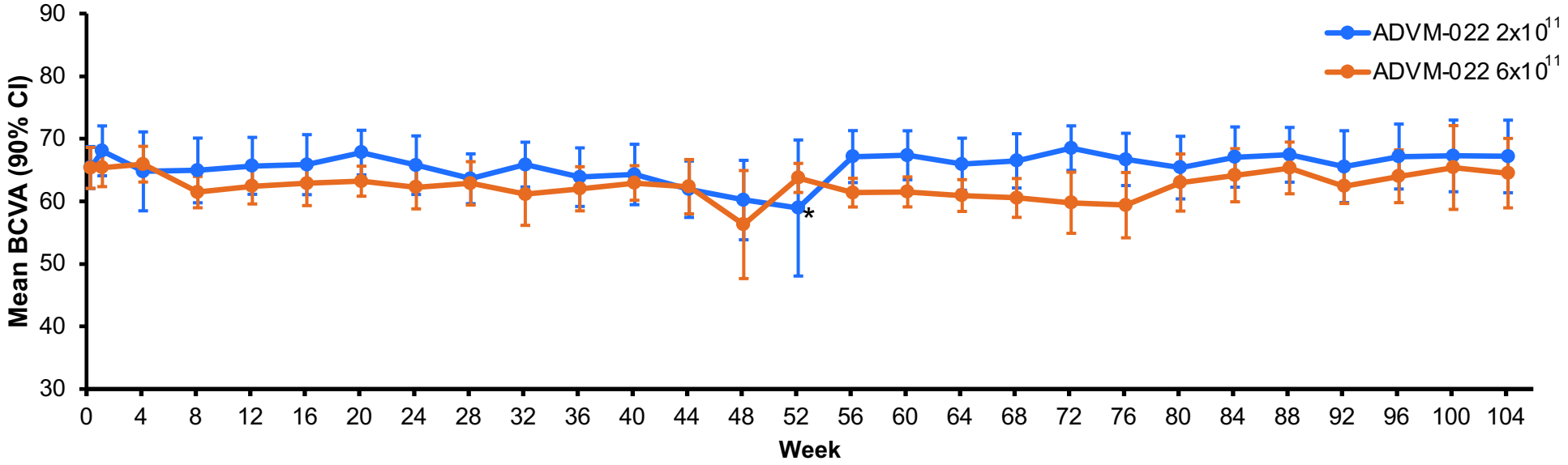
- **ADVM-022** was well tolerated in OPTIC, with dose-dependent, mild to moderate* inflammation that was responsive to topical corticosteroids
  - No participants in the $2x10^{11}$ vg/eye cohorts required any topical corticosteroids to treat inflammation at most recent follow-up
- **No** vasculitis, retinitis, choroiditis, vascular occlusions or endophthalmitis
- **No** clinically relevant low IOP (Hypotony) events observed at either dose
- Across all cohorts, most ADVM-022-related ocular AEs were mild (82.6%) to moderate (16.7%)

AC, aqueous cells; SAE, serious adverse event; VC, vitreous cells.
**Mild inflammation: trace, 0.5+, 1+ and 2+ anterior chamber cell/flare, or trace, 0.5+, 1+ and 2+ vitreous cells; moderate inflammation: +3 anterior chamber cell/flare, or 3+ vitreous cells; severe inflammation: +4 anterior chamber cell/flare, or 4+ vitreous cells*

Data Cut: Feb 24, 2022

ADVM-022 Maintains or Improves BCVA and CST Through 2 Years

Mean BCVA (90% CI) by Cohort and Week

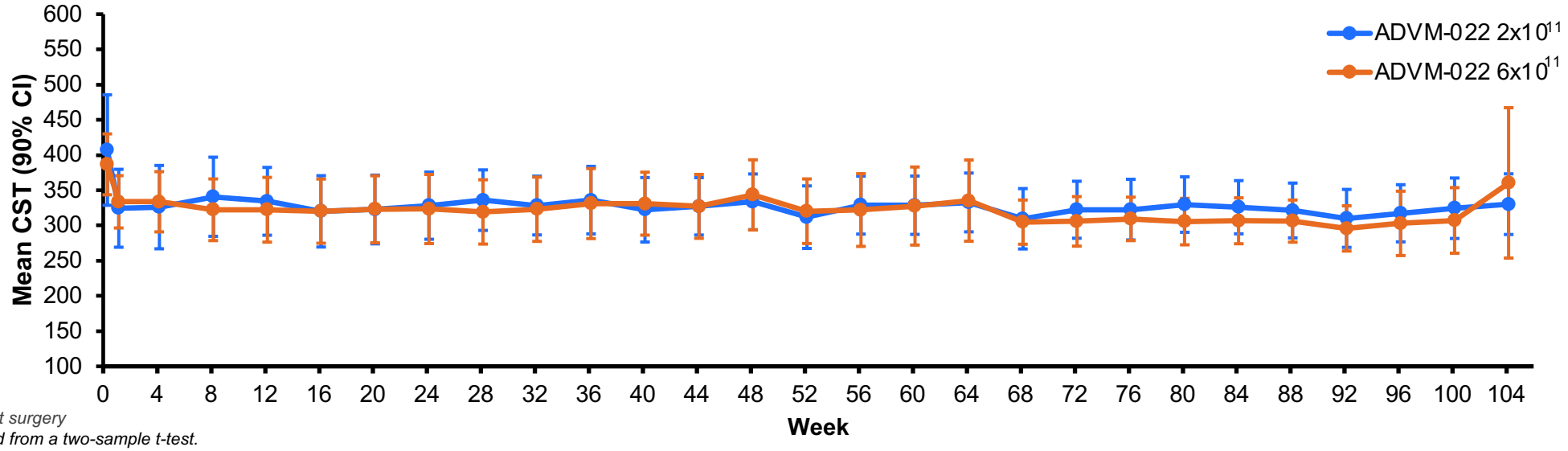


Mean BCVA (letters) change from baseline to last visit (90% CI)

+0.2 (-4.6, 5.0)
2x10^{11} vg/eye

+0.3 (-2.5, 3.2)
6x10^{11} vg/eye

Mean CST (90% CI) by Cohort and Week



Mean CST (µm) change from baseline to last visit (90% CI)

-55.7 (-90.6, -20.8)
p = 0.014**
6x10^{11} vg/eye

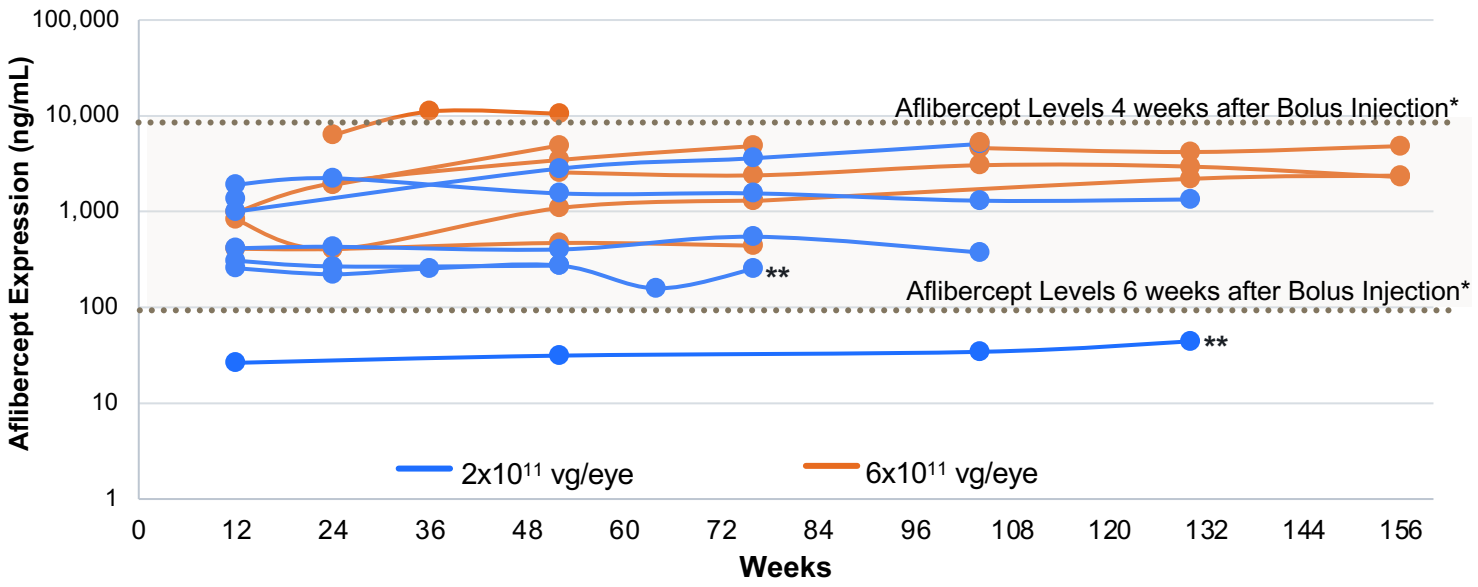
-95.9 (-156.5, -35.3)
p = 0.015**
2x10^{11} vg/eye

**Cataract surgery*
***Derived from a two-sample t-test.*

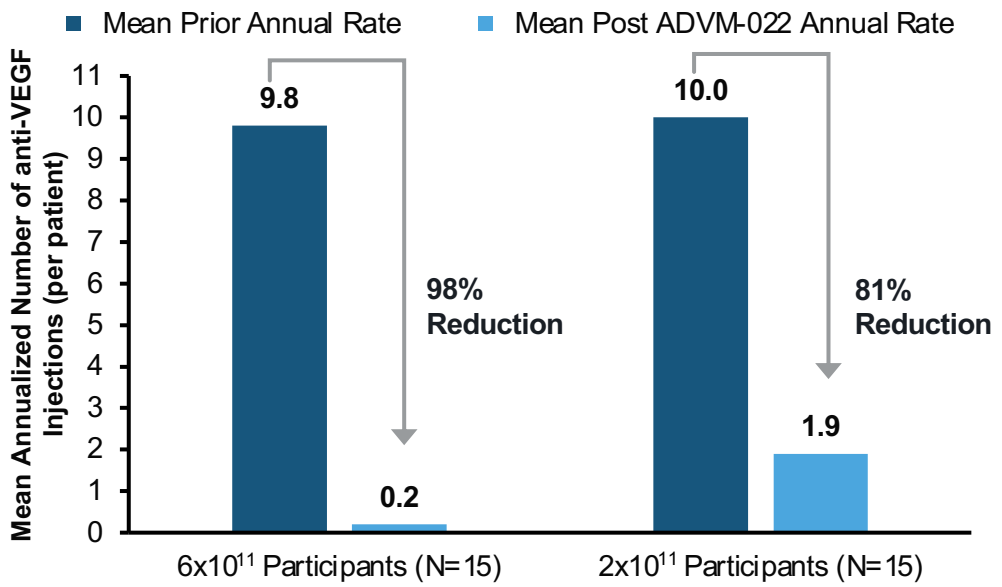
Data Cut: Feb 24, 2022

Continuous Aflibercept Protein Expression Following ADVM-022 Meaningfully Reduces Annualized Anti-VEGF Injections

Aflibercept Expression - Individual Participant Plots



Reduction in Annualized Anti-VEGF Injections

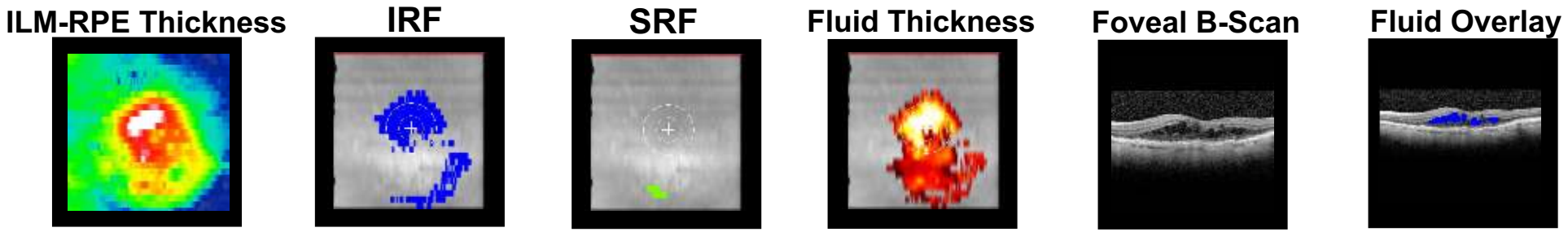


*Modeled based on Do et al. Retina 2020; 40:643-647.
** Participant received supplemental aflibercept injections
Protocol amendment for aqueous sample collection for participants that consented. To isolate the effect of ADVM-022, samples that were collected within 2 months of supplemental aflibercept are not shown.
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) = (numbers of aflibercept IVTs since ADVM-022) / (days from ADVM-022 to the last study follow-up / 365.25).
VEGF, vascular endothelial growth factor.

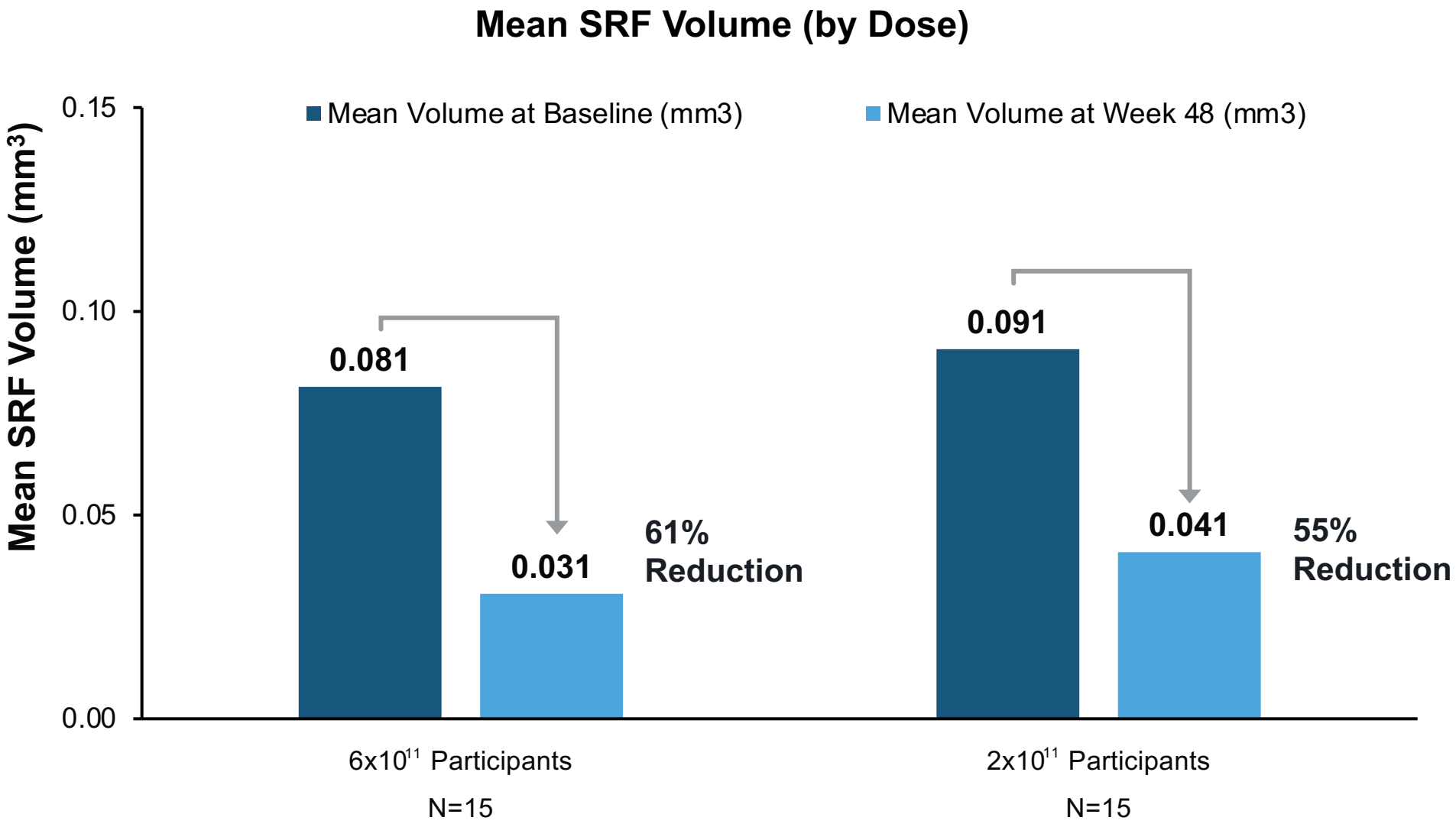
Impact of a Single IVT Injection of ADVM-022 on Intraretinal Fluid (IRF) and Subretinal Fluid (SRF)

Methods

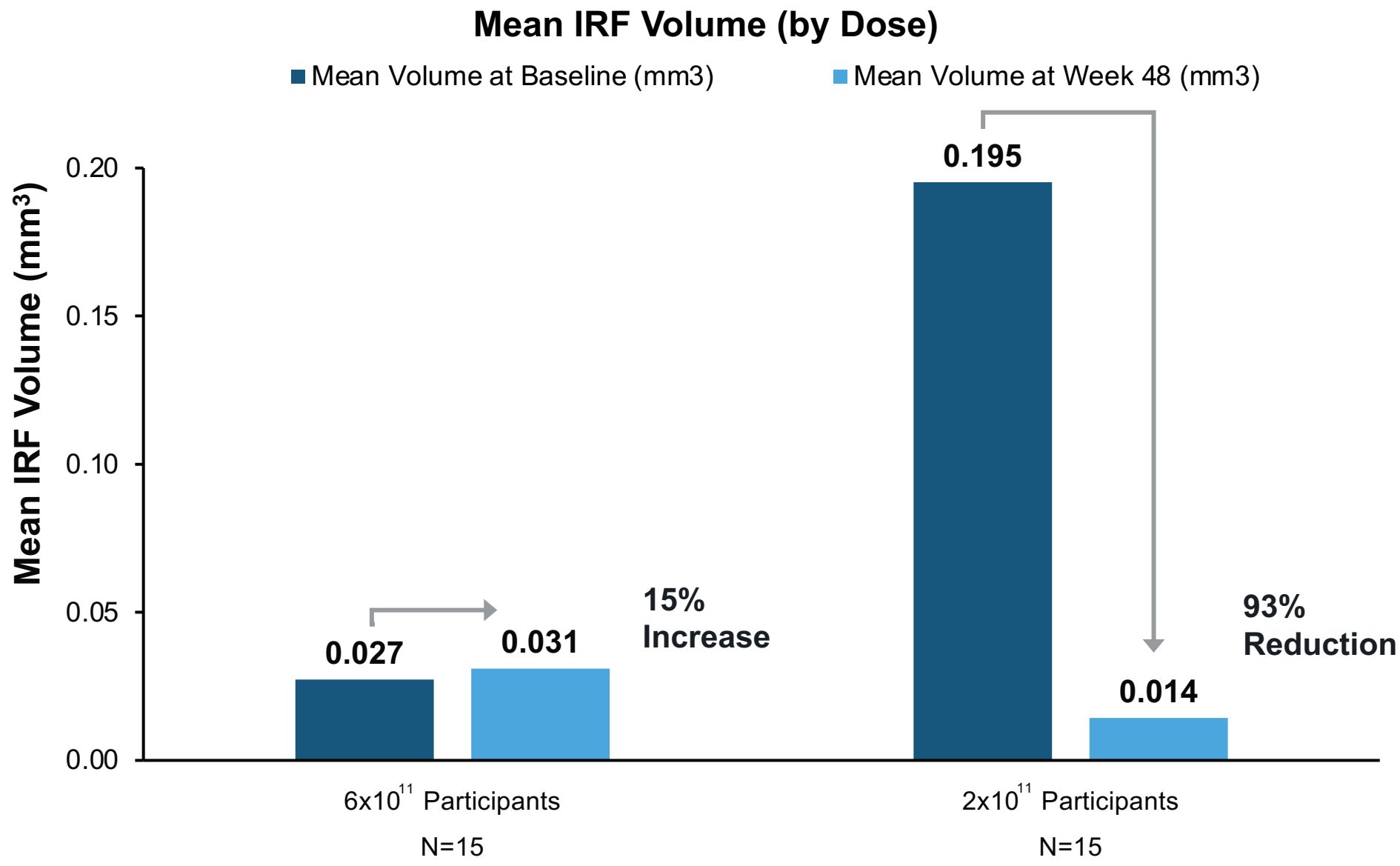
- The following analyses examine the impact of a single IVT injection of ADVM-022 gene therapy on IRF and SRF in the OPTIC Study
- Manual segmentation was performed by Justis P. Ehlers, MD at the Tony and Leona Campane Center for Excellence in Image-Guided Surgery and Advanced Imaging Research, Cole Eye Institute, Cleveland Clinic



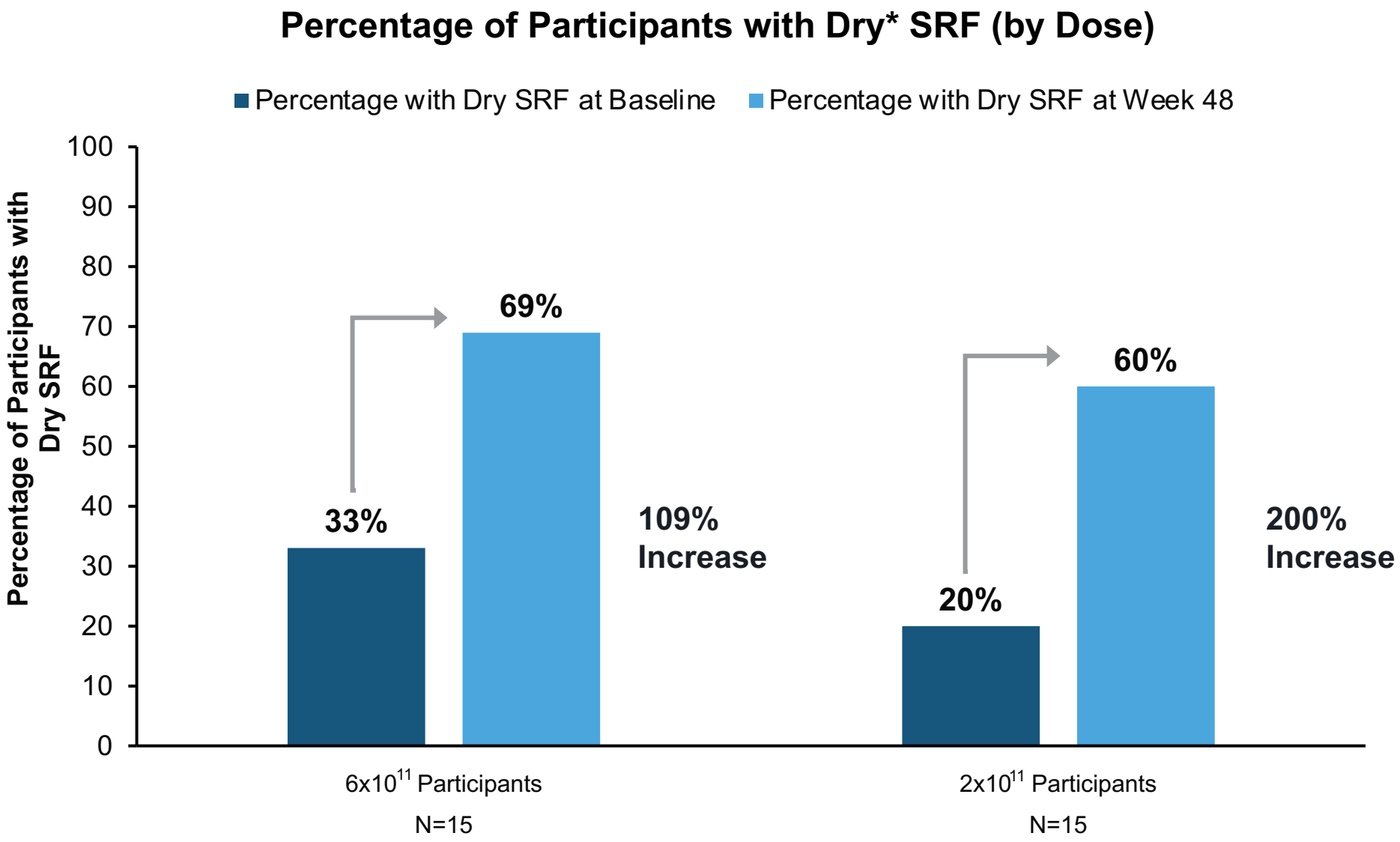
Single IVT Injection of ADVM-022 at $2x10^{11}$ Dose: 55% Reduction in Mean SRF Volume from Baseline to Week 48



Single IVT Injection of ADVM-022 at $2x10^{11}$ Dose: 93% Reduction in Mean IRF Volume from Baseline to Week 48

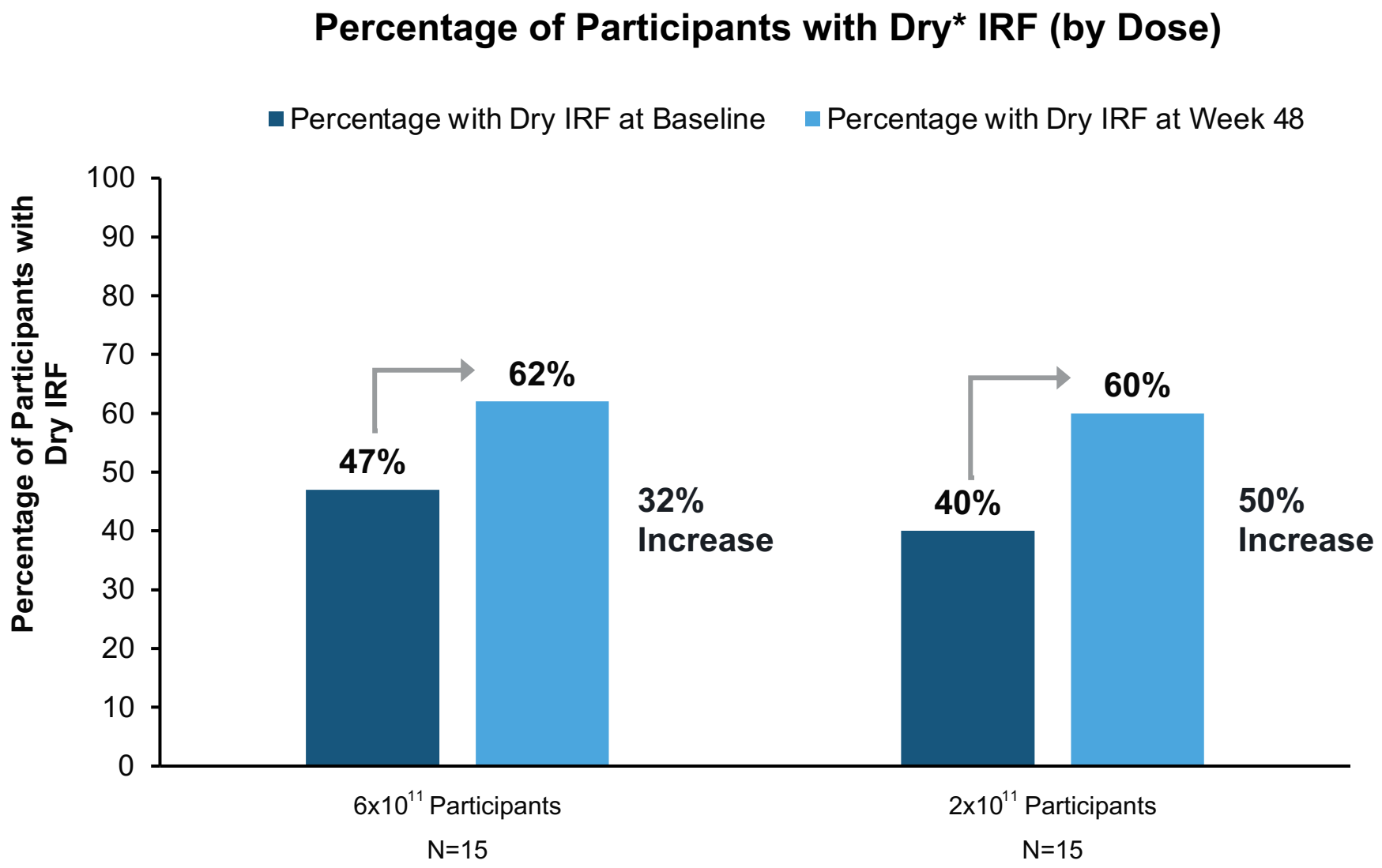


Single IVT Injection of ADVM-022 at $2x10^{11}$ Dose: 200% Increase in Percentage of Participants with Dry SRF from Baseline to Week 48



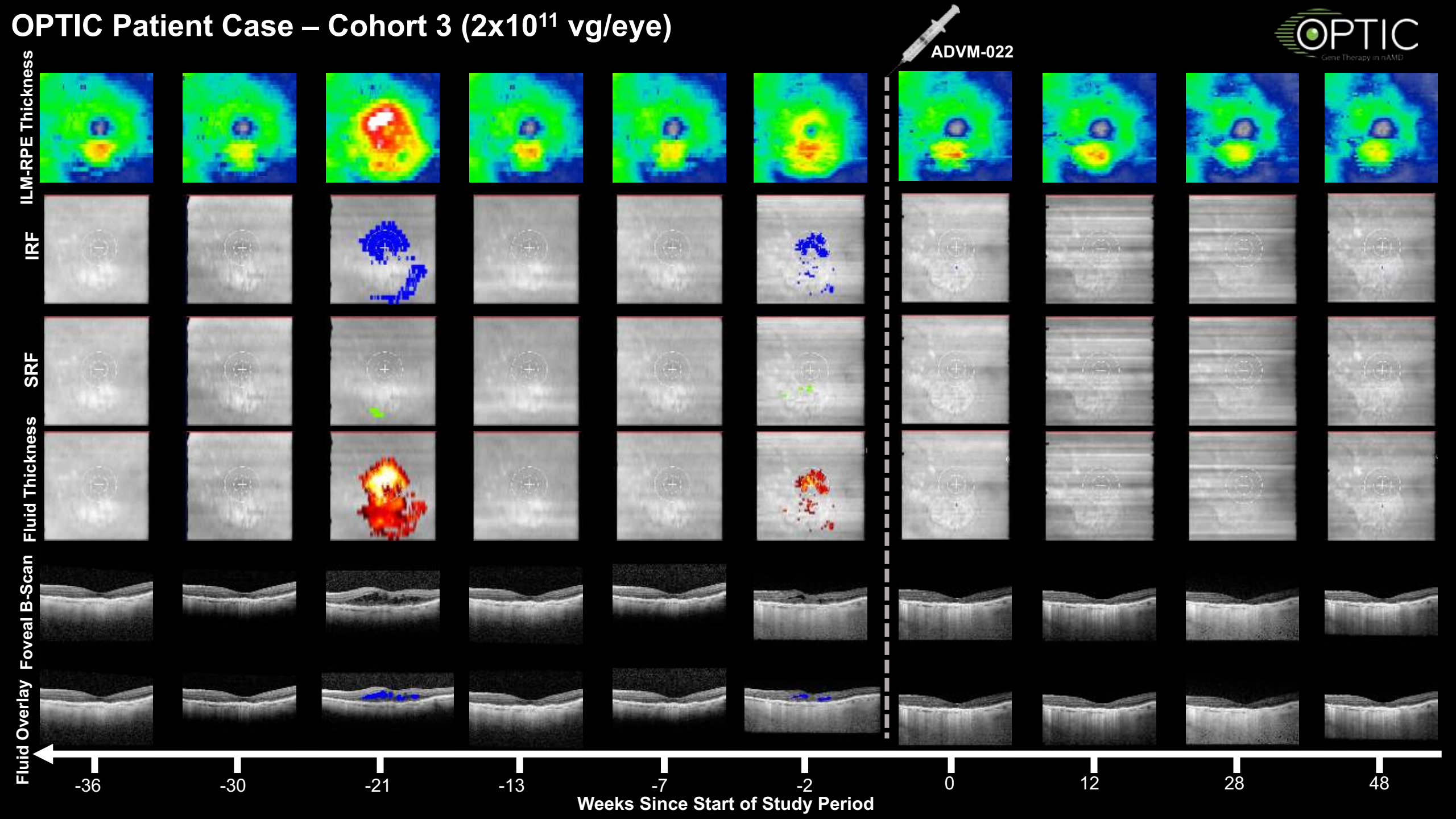
*Dry is defined as <0.0001mm^3

Single IVT Injection of ADVM-022 at $2x10^{11}$ Dose: 50% Increase in Percentage of Participants with Dry IRF from Baseline to Week 48

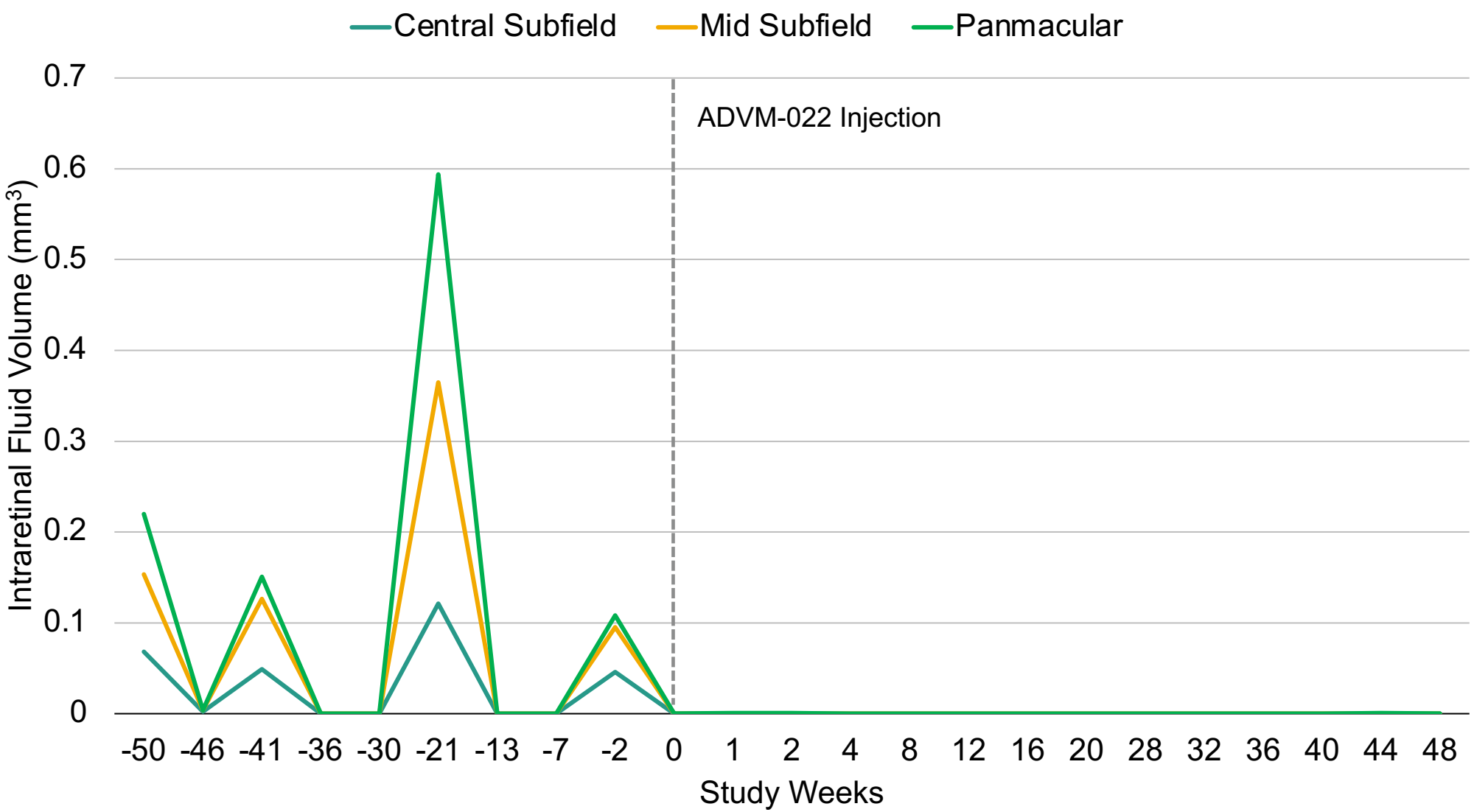


*Dry is defined as <0.0001mm^3

OPTIC Patient Case – Cohort 3 ($2x10^{11}$ vg/eye)



Patient Case – Cohort 3 ($2x10^{11}$ vg/eye): Change in Intraretinal Fluid Volume Per Region Over Time



ADVM-022 in OPTIC wet AMD Study: Key Takeaways

- **A single IVT administration of ADVM-022 delivered stable levels of aflibercept through 2 years leading to >80% reduction in annualized anti-VEGF**
- **ADVM-022 at the $2x10^{11}$ vg/eye dose meaningfully reduced fluid volume**
  - 93% reduction in IRF volume and 55% reduction in SRF volume from baseline to week 48
  - Percentage of participants with dry IRF increased from 40% to 60% and dry SRF increased from 20% to 60%
- The results of this fluid analysis further support the favorable anatomical outcomes and reduction in treatment burden previously observed in OPTIC
- **Stable, persistent aflibercept expression may correlate to better fluid control**
- ADVM-022 was well tolerated in OPTIC. Inflammation was dose-dependent, mild to moderate, and responsive to topical corticosteroids
- Limitations of this analysis include small sample size (n=30)
- The results from the OPTIC study support the further development of ADVM-022 for nAMD
  - **The Phase 2 LUNA study is now enrolling and is evaluating the $2x10^{11}$ vg/eye dose as well as a lower $6x10^{10}$ vg/eye dose. The first participant was dosed 13Sep2022**

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