



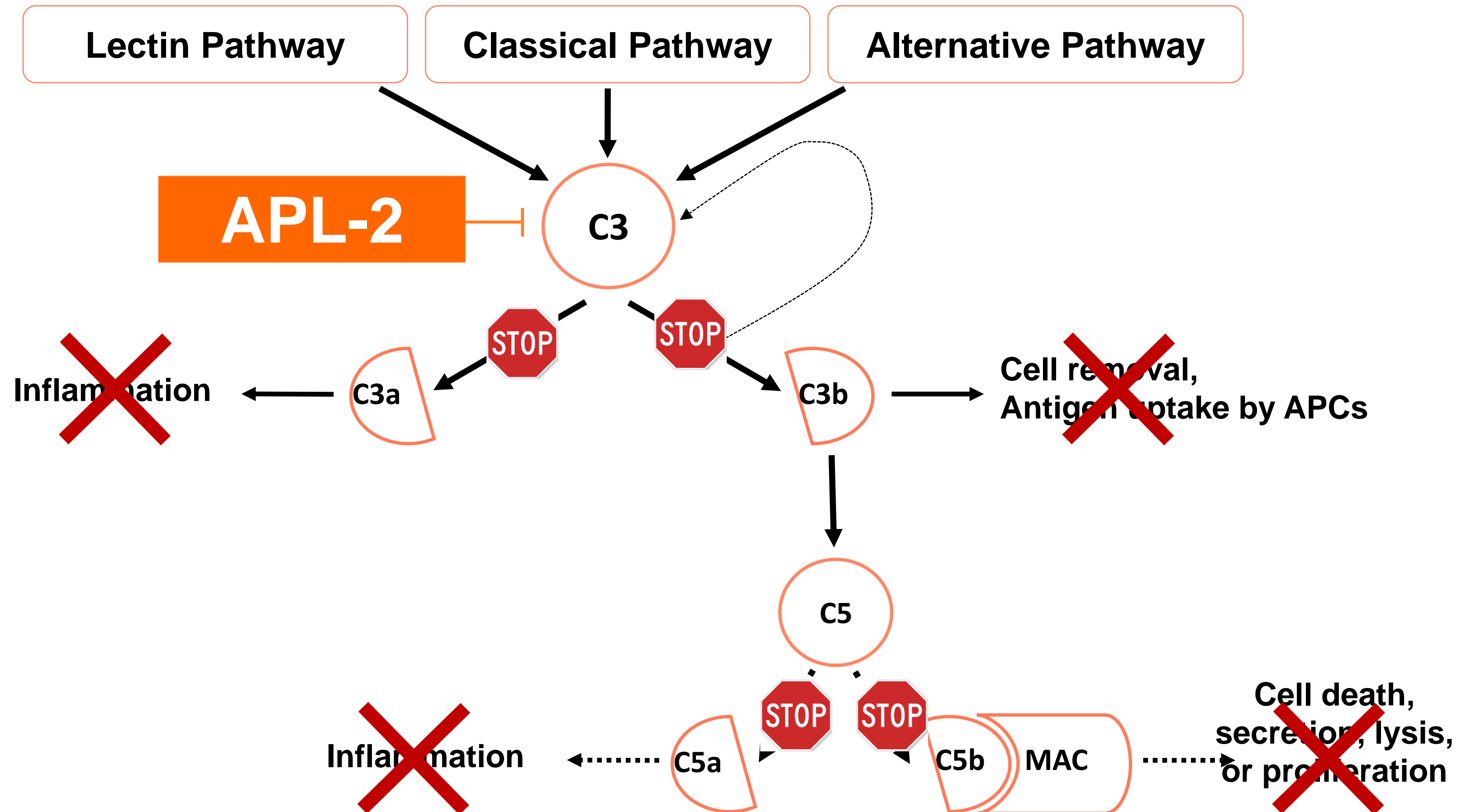
APL-2 (pegcetacoplan)  
Geographic atrophy  
Preliminary 18-month results

Rishi P. Singh, MD  
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Associate Professor of Ophthalmology, Case Western Reserve University  
Medical Director, Clinical Systems Office

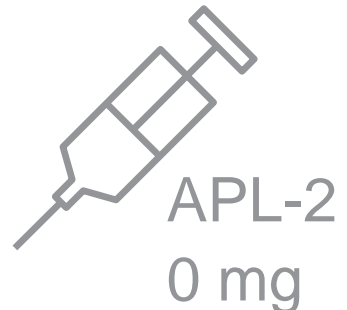
# Financial disclosures

- Consultant – Genentech, Regeneron, Novartis/Alcon, Optos, Zeiss
- Sponsored research support – Apellis, Genentech, Regeneron , Alcon/Novartis, Clearside

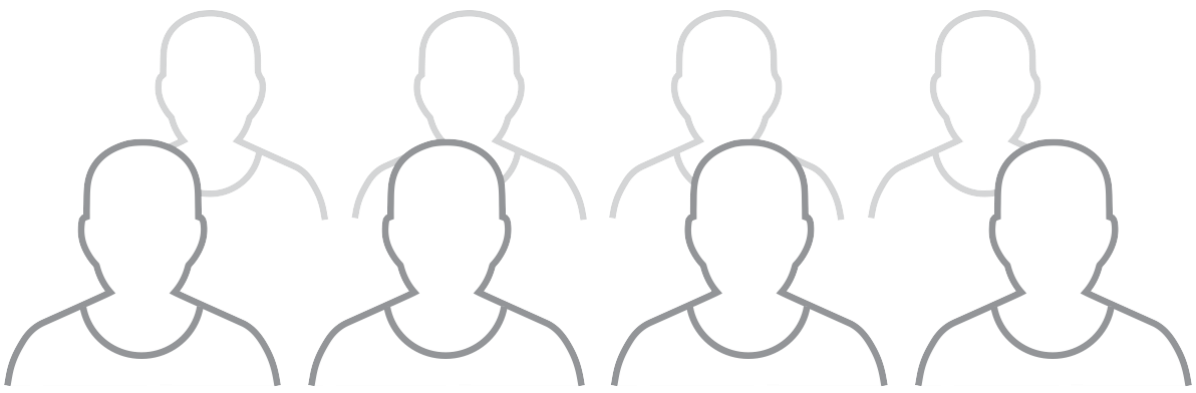
# The Complement Pathway and Geographic Atrophy



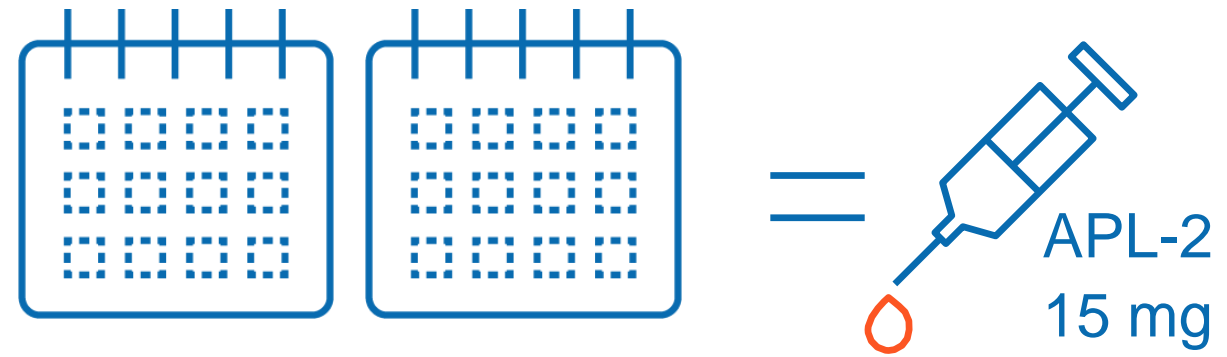
# FILLY - Phase 2 study of APL-2 in Geographic Atrophy



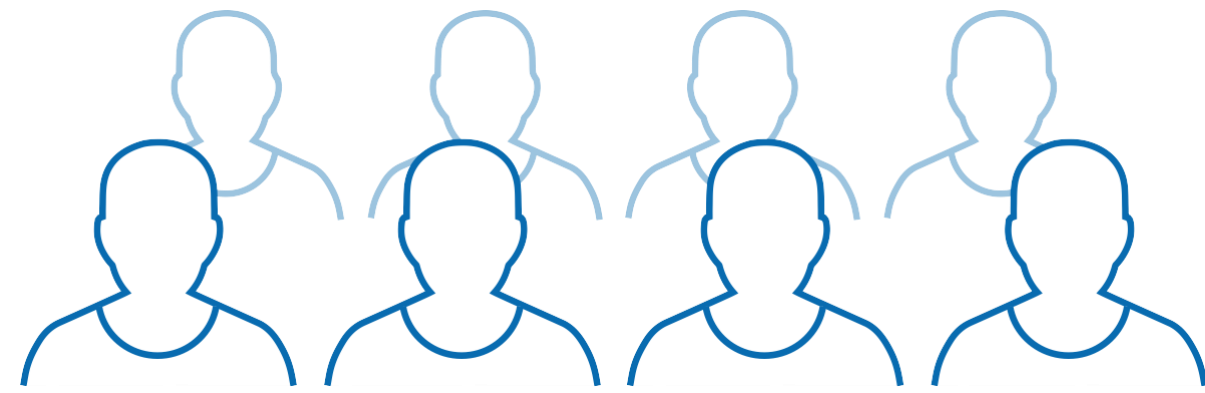
Sham injections



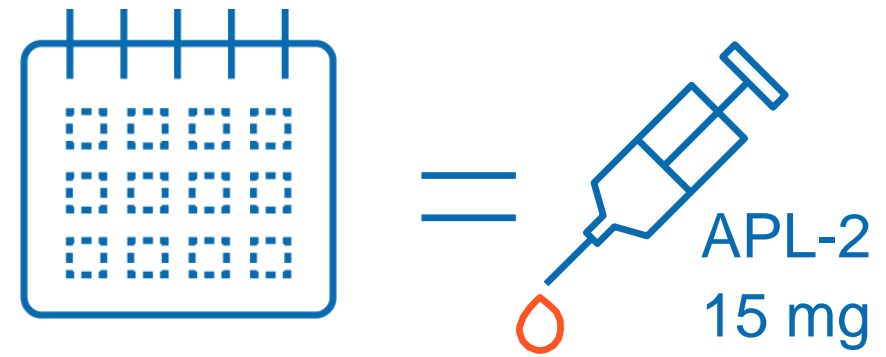
**Sham group, n=81**



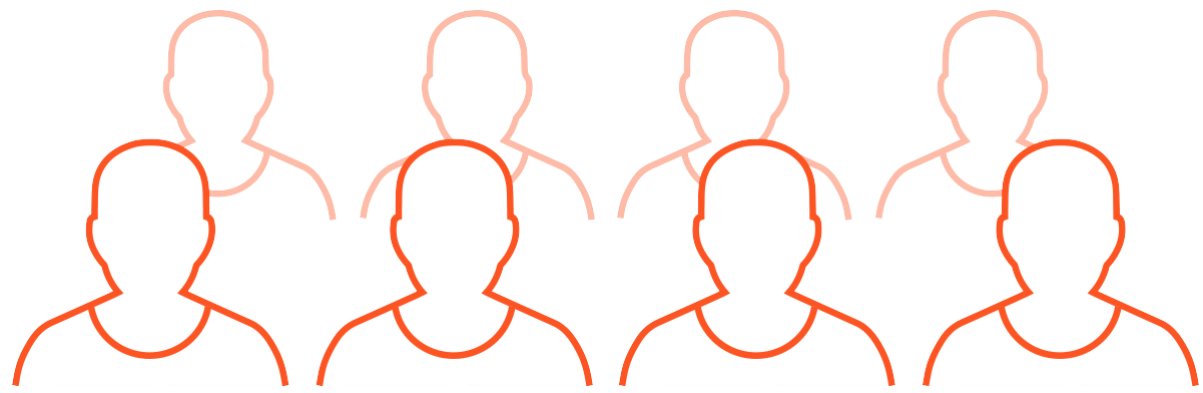
APL-2 injections every other month



**Active group 1, n=79**

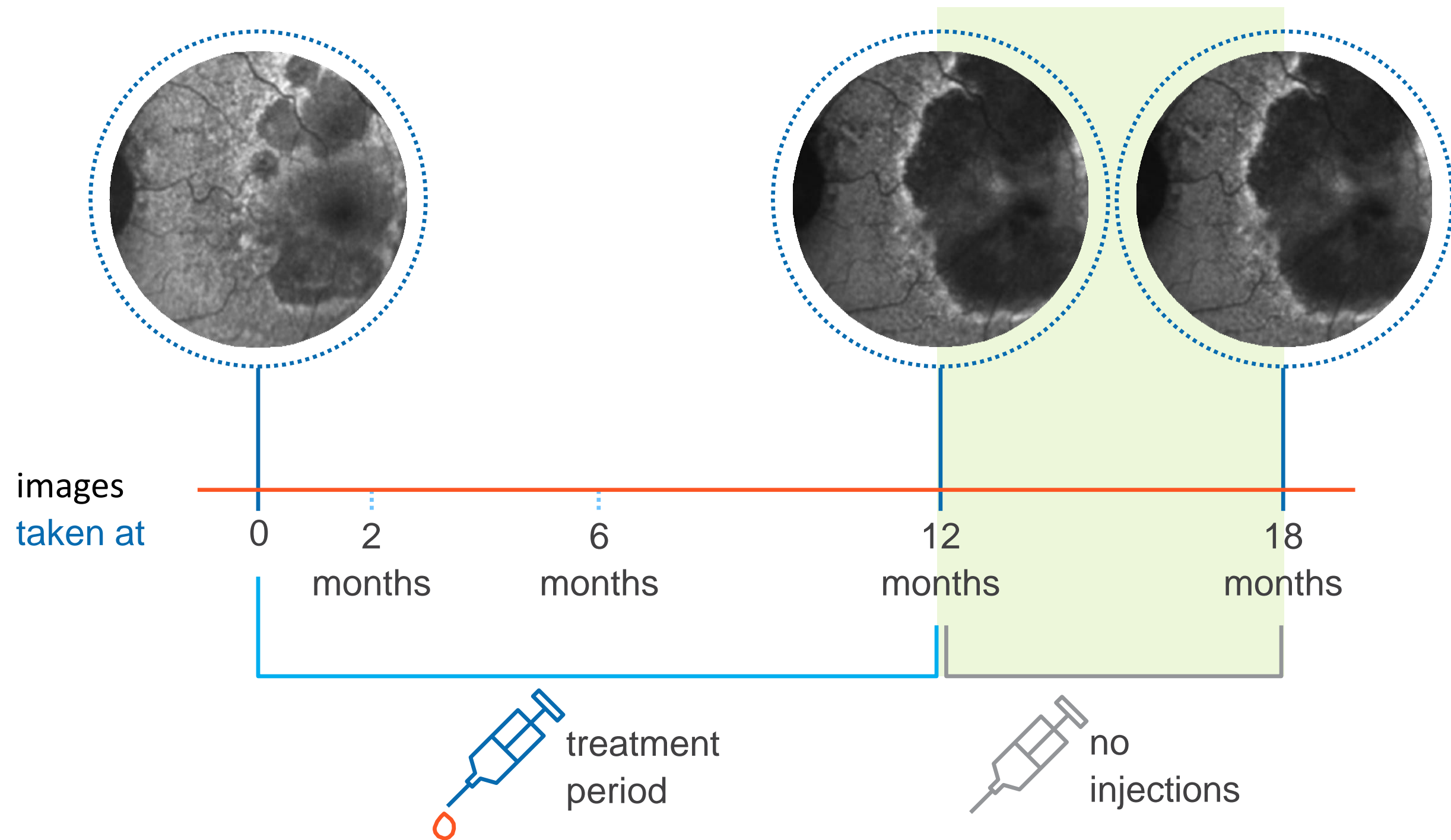


APL-2 injections every month



**Active group 2, n=86**

# FILLY – timeline and endpoints



**Primary efficacy endpoint is the primary registration endpoint**

Change in geographic atrophy (GA) lesion size from baseline to month 12.

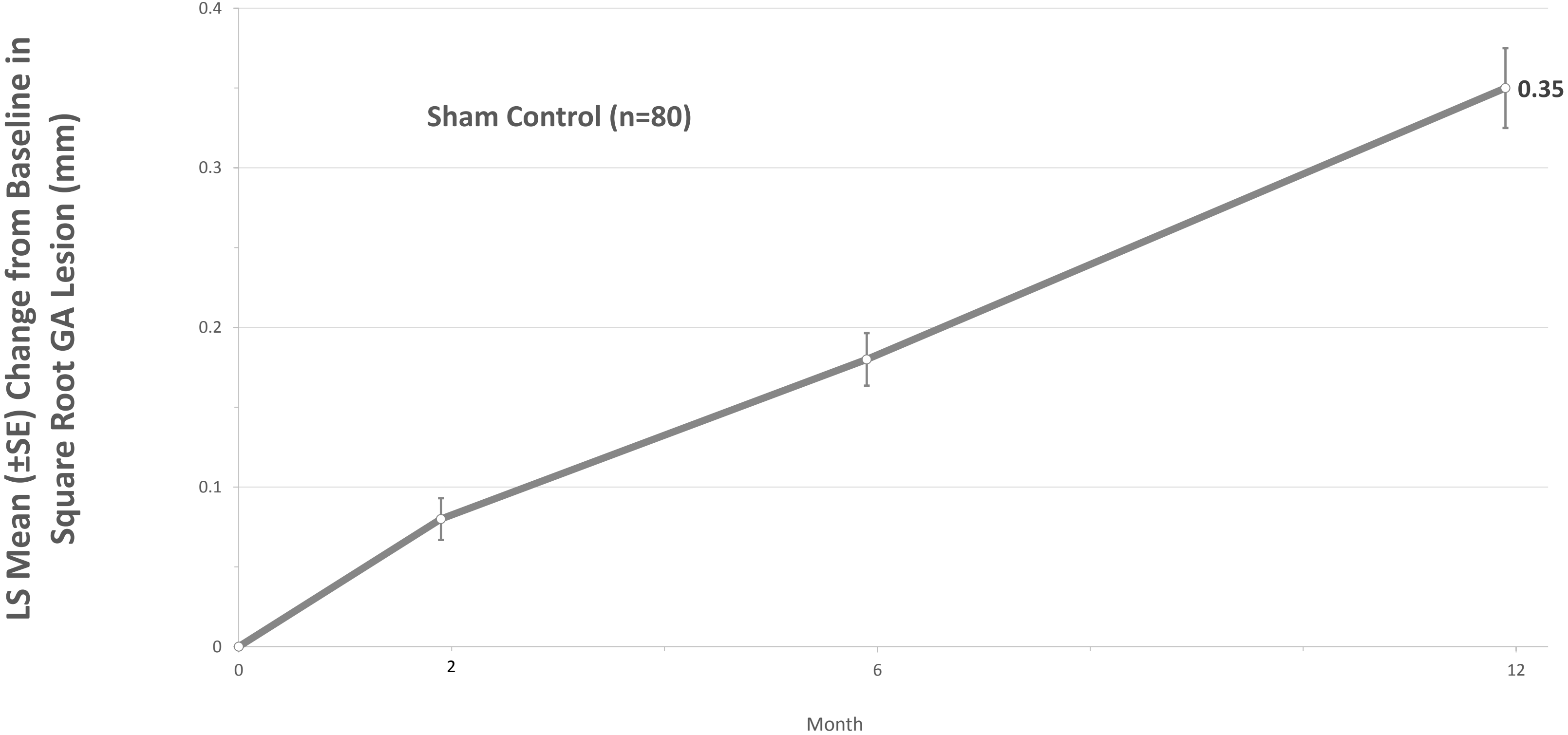
**Primary safety endpoint**

Number and severity of local and systemic treatment emergent adverse events (TEAEs).

# Baseline Characteristics

|  | APL-2<br>Monthly<br>N=86 | APL-2<br>Every Other<br>Month<br>N=79 | Sham<br>Pooled<br>N=81 |
|--|--------------------------|---------------------------------------|------------------------|
| Bilateral GA, n (%)                        | 71 (85.5%)               | 64 (82.1%)                            | 72 (90.0%)             |
| History of CNV in Fellow Eye, n (%)        | 36 (41.9%)               | 28 (35.4%)                            | 29 (35.8%)             |
| GA lesion size, mean, mm <sup>2</sup> (SD) | 8.0 (3.8)                | 8.9 (4.5)                             | 8.2 (4.1)              |
| BCVA score, mean letters (SD)              | 59.8 (15.7)              | 58.4 (16.0)                           | 59.8 (17.2)            |
| BCVA score (Snellen equivalent)            | 20/63                    | 20/80                                 | 20/63                  |
| LL-BCVA score, mean letters (SD)           | 36.3 (16.6)              | 31.4 (17.1)                           | 33.6 (17.8)            |

# Primary Endpoint: GA Lesion Growth

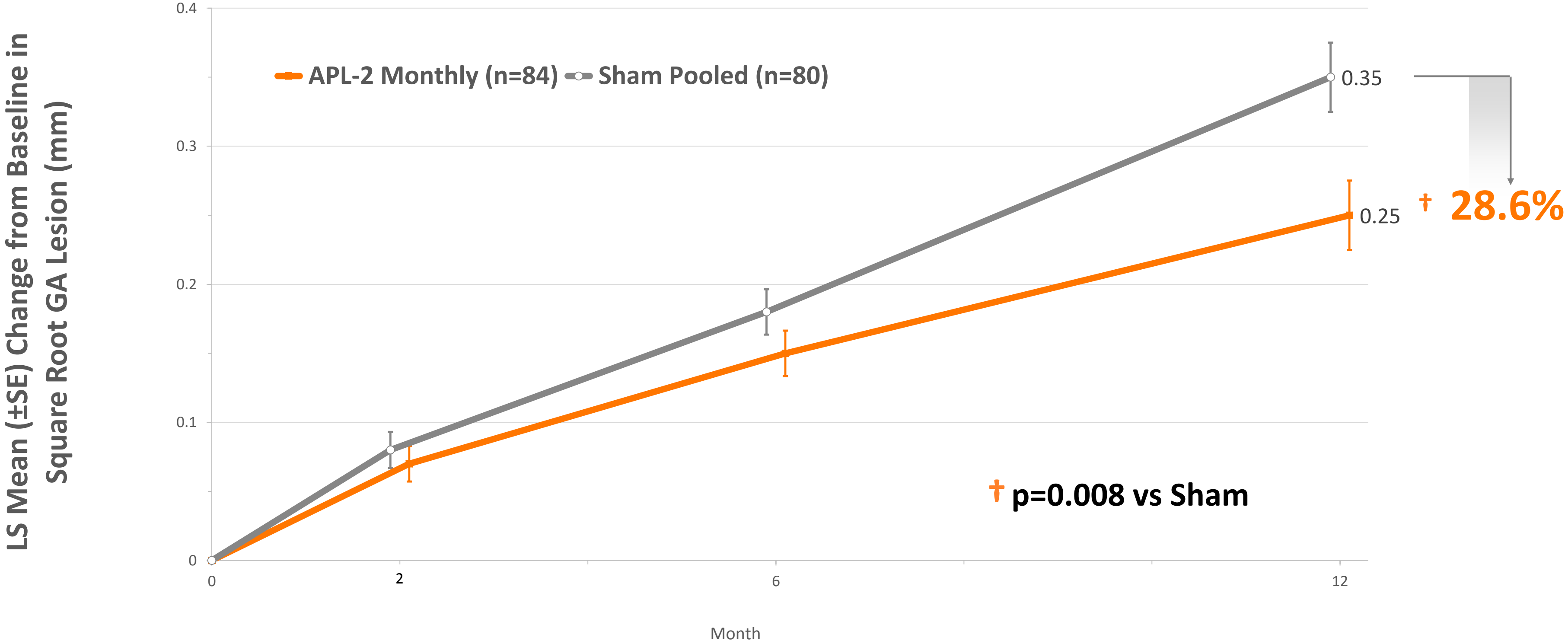


**Modified Intent to Treat population (mITT), Observed, Mixed-Effect Model**

A mixed effect model with main effects of treatment, visit and GA lesion at baseline, and interactions of treatment × visit, visit × baseline.

mITT = All subjects receiving at least one injection and having at least one FAF image after day 1

# Primary Endpoint: GA Lesion Growth

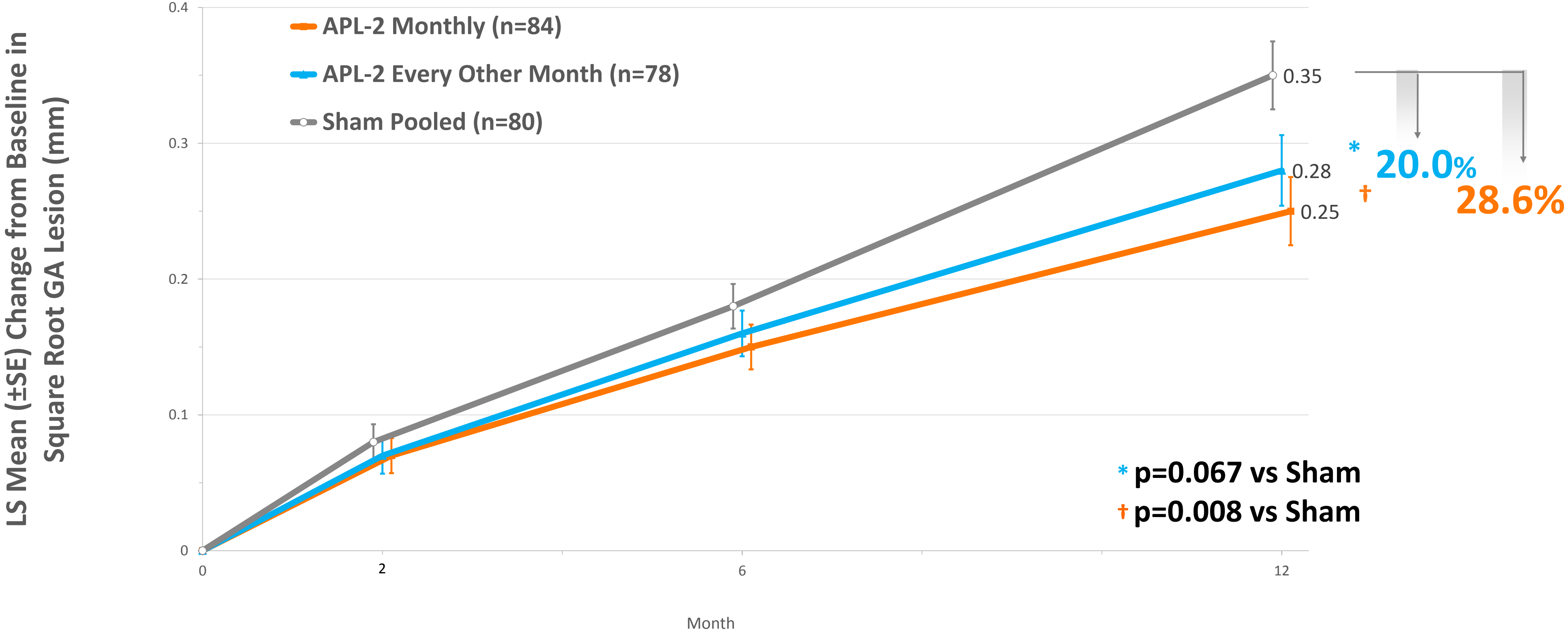


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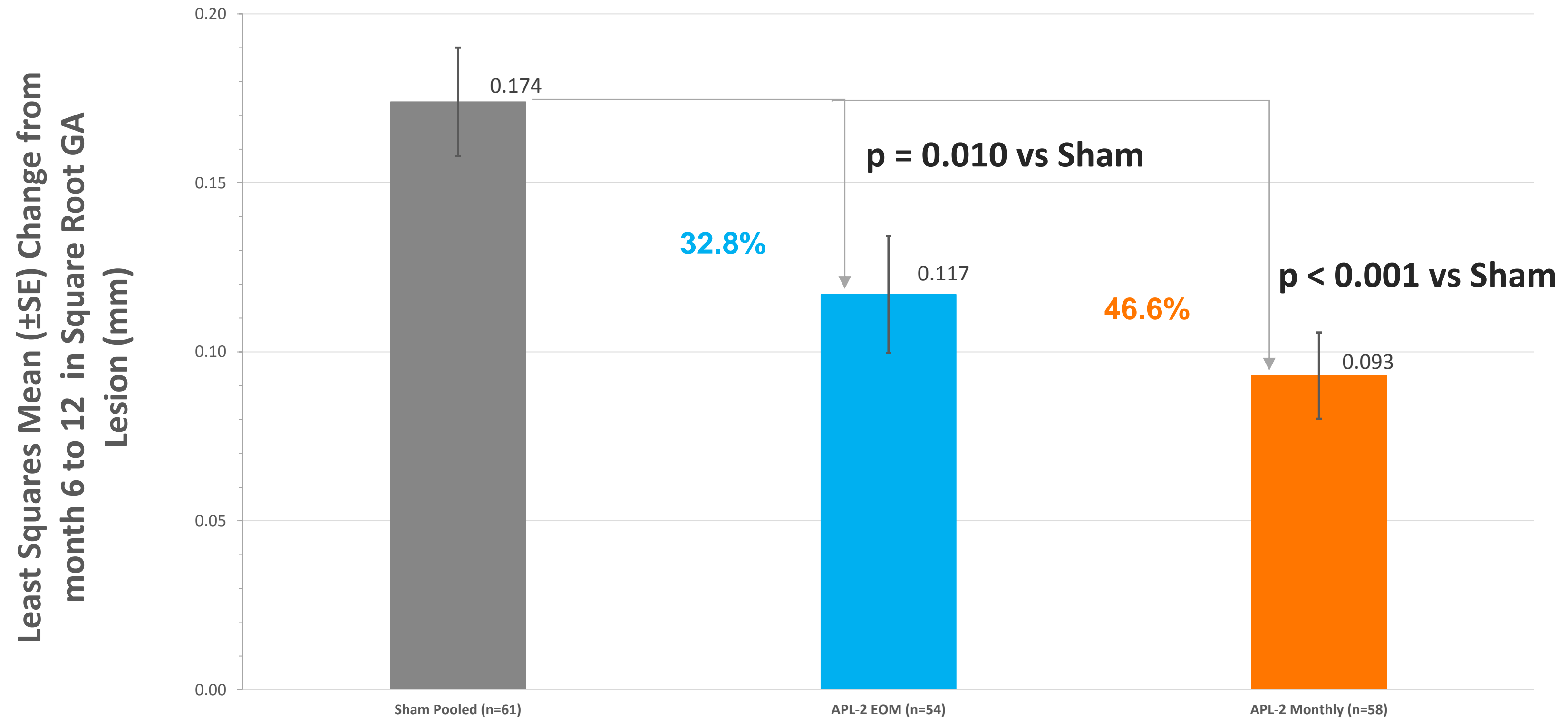


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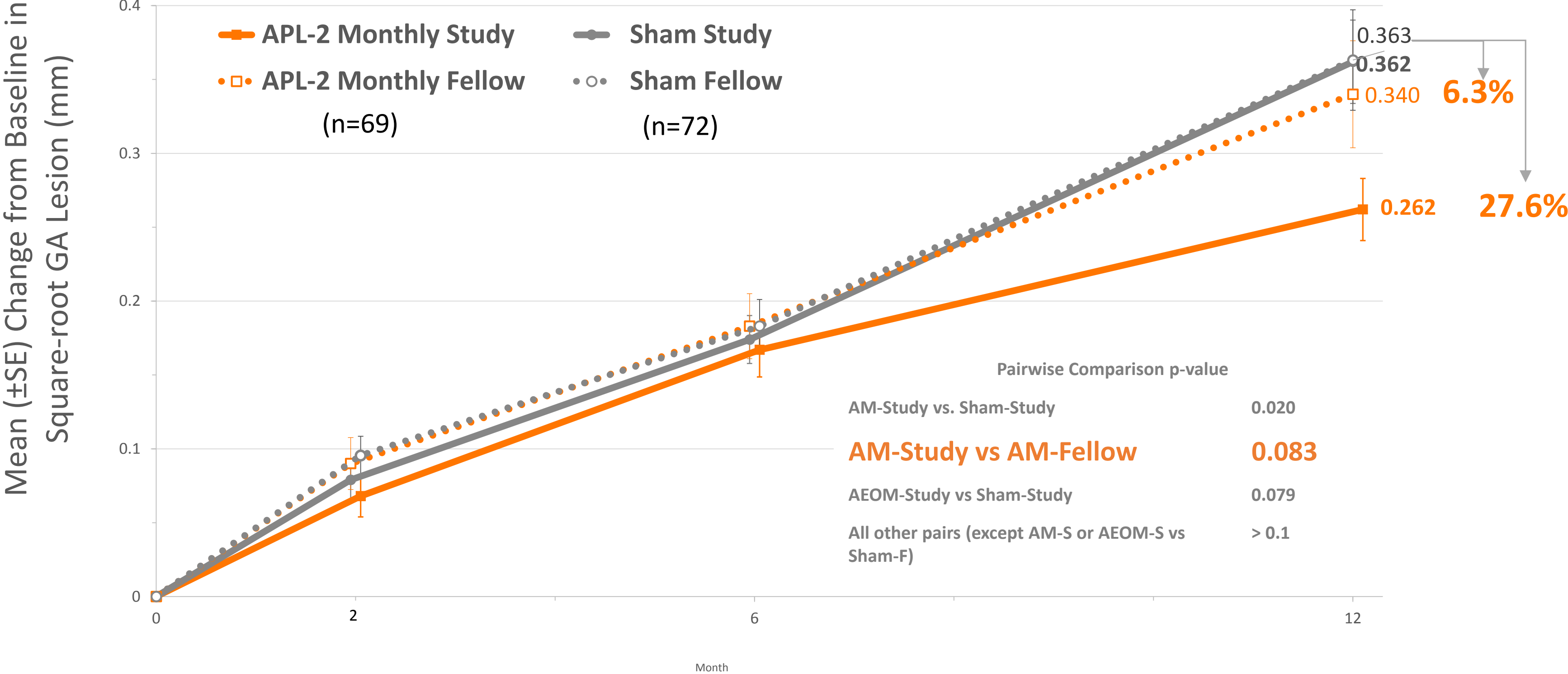
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# Post hoc analysis: greater reduction in GA lesion growth from month 6 to 12



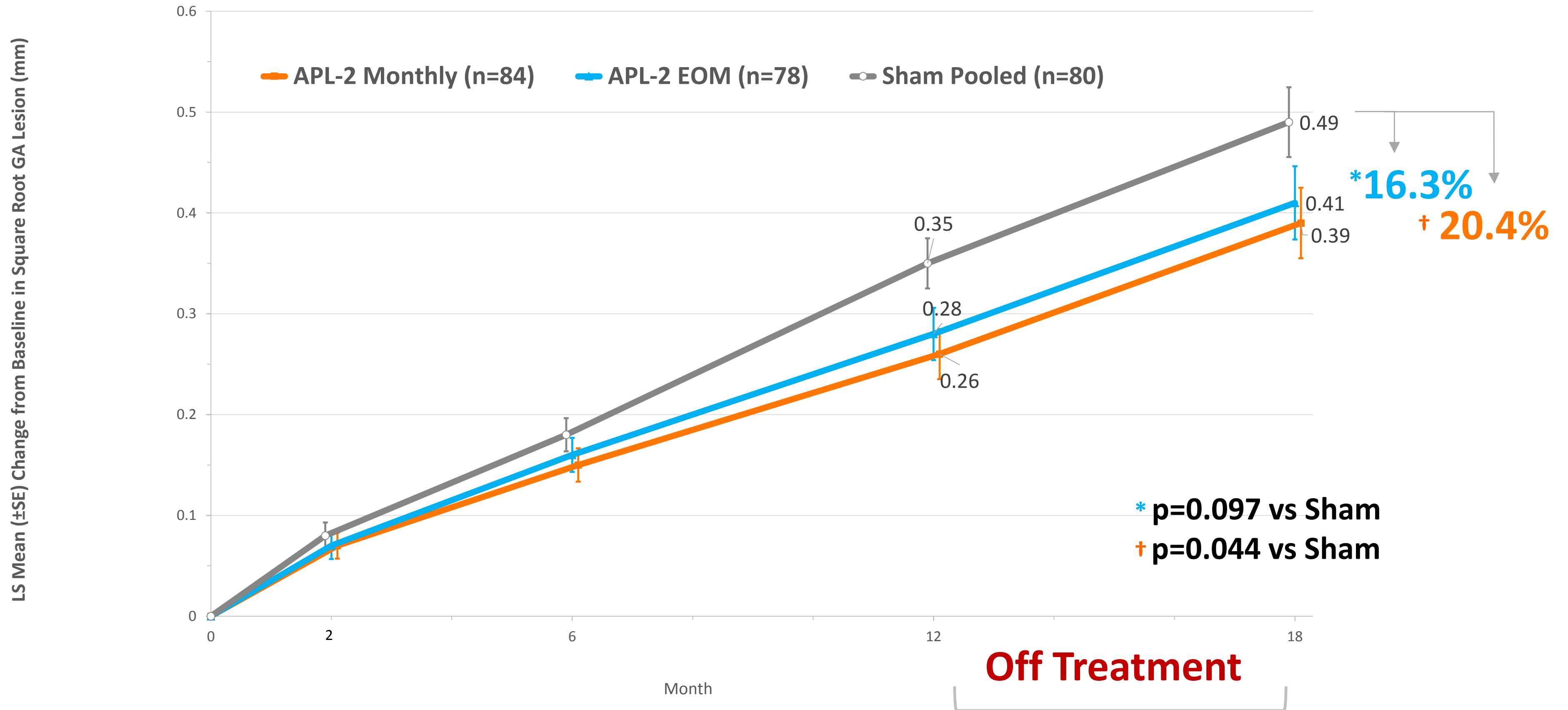
Data from subjects with a measurable GA lesion size at both Months 6 & 12. Data as of August 24, 2017

# Post hoc analysis: in bilateral GA, monthly APL-2 reduced GA growth compared to contralateral eye



mITT-Bilateral GA, Observed, ANOVA at Month 12. Data as of August 24, 2017

# GA Lesion Growth to 18 Months

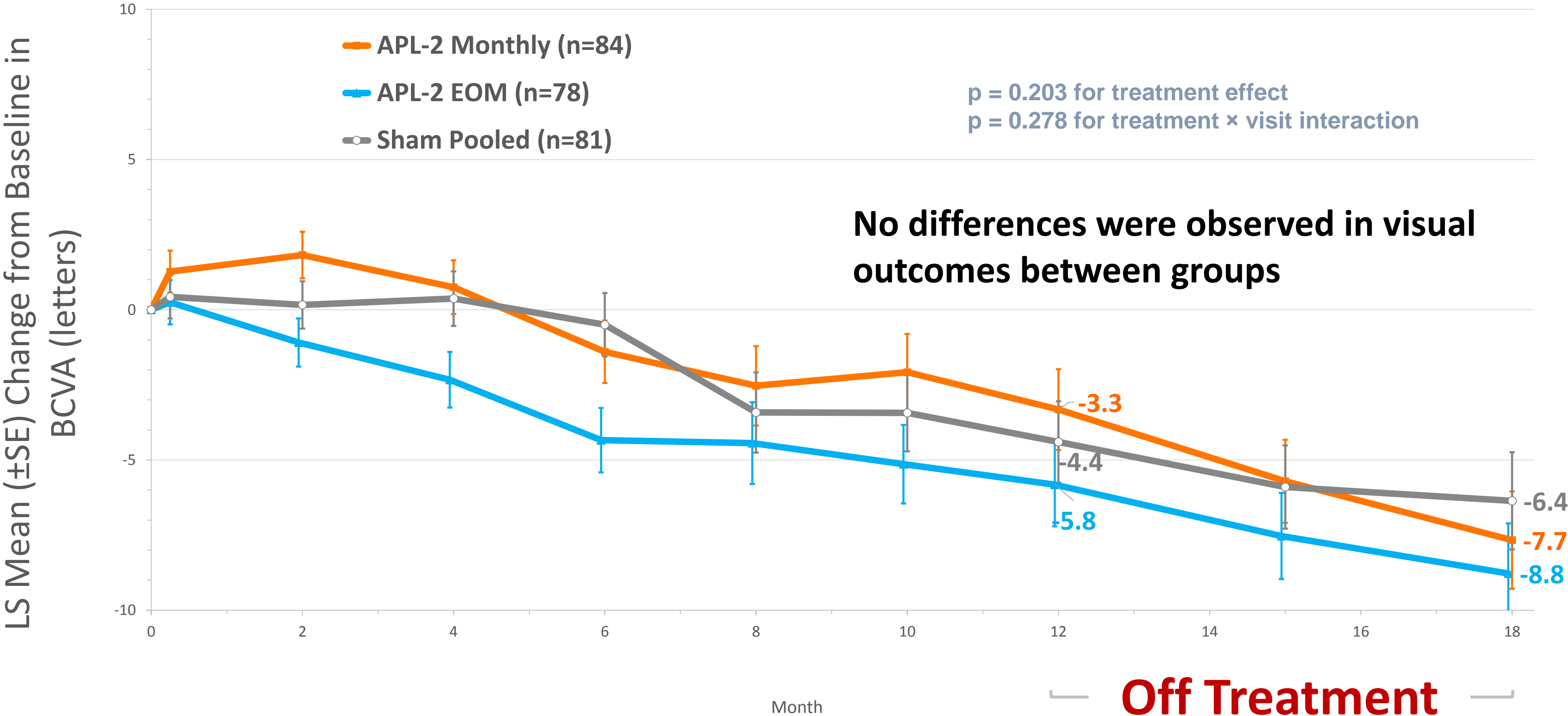


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# Best Corrected Visual Acuity

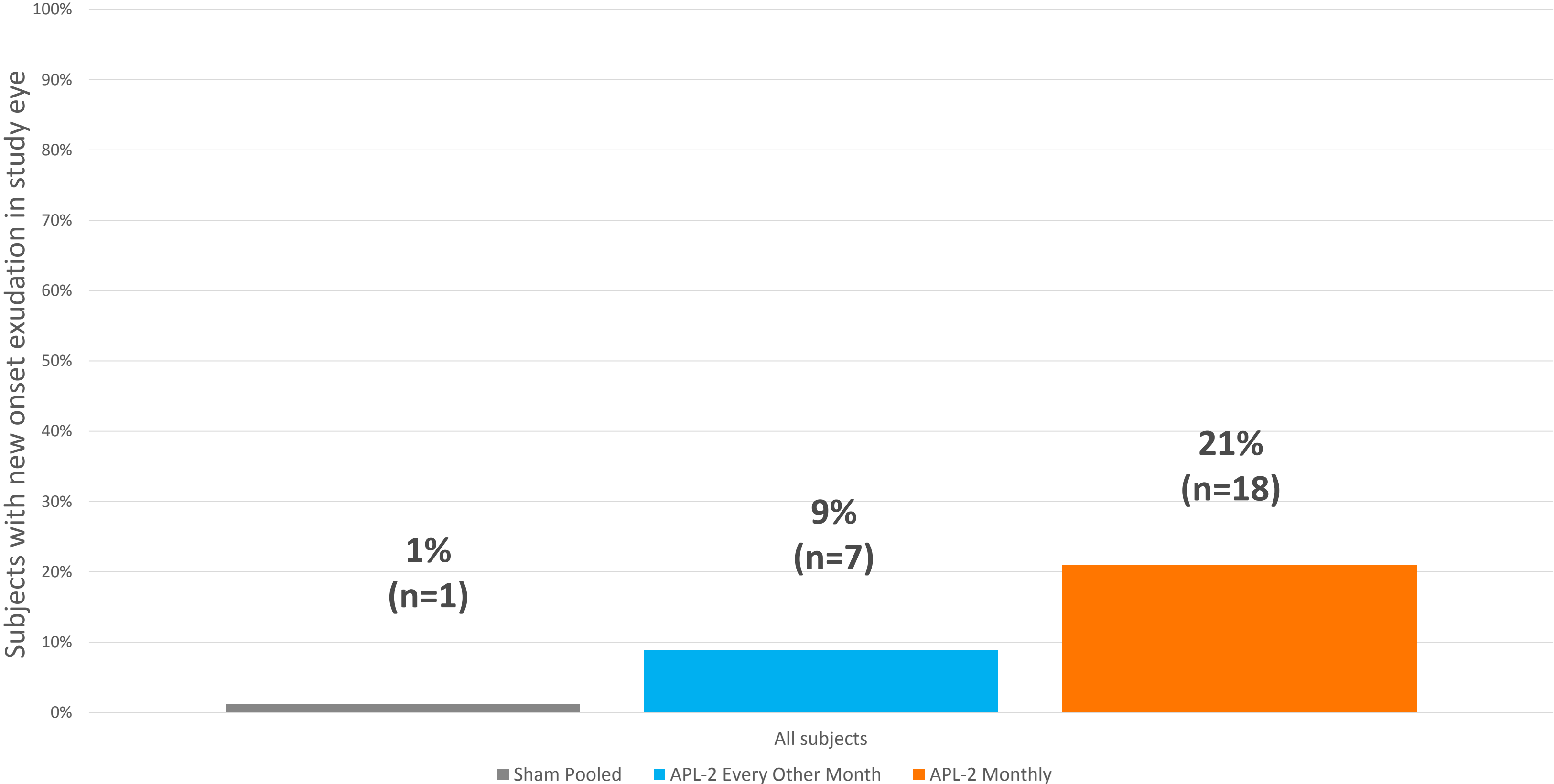


Modified Intent to Treat population (mITT), Observed, Mixed-Effect Model


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mITT = All subjects receiving at least one injection and having at least one FAF image after day 1

# New Onset Exudation – 18 months



# Adverse Event Profile

| Adverse Event<br>n (%) of subjects with events  | APL-2 Monthly<br>N=86 | APL-2 Every Other<br>Month<br>N=79 | Sham Pooled<br>N=81 |
|---|-----------------------|------------------------------------|---------------------|
| Ocular SAEs in study eye*   | 4 (4.7%)              | 2 (2.5%)                           | 1 (1.2%)            |
| Systemic (non-ocular) SAEs  | 19 (22.1%)            | 24 (30.4%)                         | 23 (28.4%)          |
| Treatment related ocular AEs in the study eye   | 22 (25.6%)            | 11 (13.9%)                         | 0                   |
|  New onset exudation | 18 (20.9%)            | 7 (8.9%)                           | 1 (1.2%)            |
| Treatment related systemic (non-ocular) AEs   | 0                     | 0                                  | 0                   |
| Ocular SAEs   | APL-2 Monthly<br>N=86 | APL-2 EOM<br>N=79                  | Sham Pooled<br>N=81 |
| Endophthalmitis*  | 2 (2.3%)              | 1 (1.3%)                           | 0                   |
| IOP increased   | 1 (1.2%) <sup>†</sup> | 1 (1.3%)                           | 0                   |
| Retinal detachment  | 1 (1.2%)              | 0                                  | 0                   |
| Visual impairment   | 0                     | 0                                  | 1 (1.2%)            |

\*2 culture positive for coagulase-negative Staphylococcus. 1 culture negative in the monthly group.

†2 events in a subject

# Possible explanations for APL-2 associated exudation

- APL-2 induces vascular exudation in the absence of neovascularization (VEGF-Like effect)
  - FA was not required on conversion to exudative AMD so no confirmation this was truly from CNV complex
- APL-2 induces neovascularization and exudation
- APL-2 induces exudation for pre-existing subclinical neovascularization
  - FA at baseline would have missed subclinical lesions
  - ICG angiography and OCT angiography were not performed in the study
  - Structural OCT was performed – double layer sign



## Optical Coherence Tomography Angiography of Asymptomatic Neovascularization in Intermediate Age-Related Macular Degeneration

Luiz Roisman, MD,<sup>1,2</sup> Chieh-Li Chen, PhD,<sup>3</sup> Andrew Miller, BS,<sup>1</sup> et al.

**Purpose:** To determine if OCT angiography identifies subclinical types of neovascularization (iAMD).

**Design:** Prospective, observational study.

**Participants:** Patients with intermediate AMD in their fellow eyes.

**Methods:** The patients underwent fluorescein angiography and OCT angiography.

**Main Outcome Measures:** Identification of neovascularization.

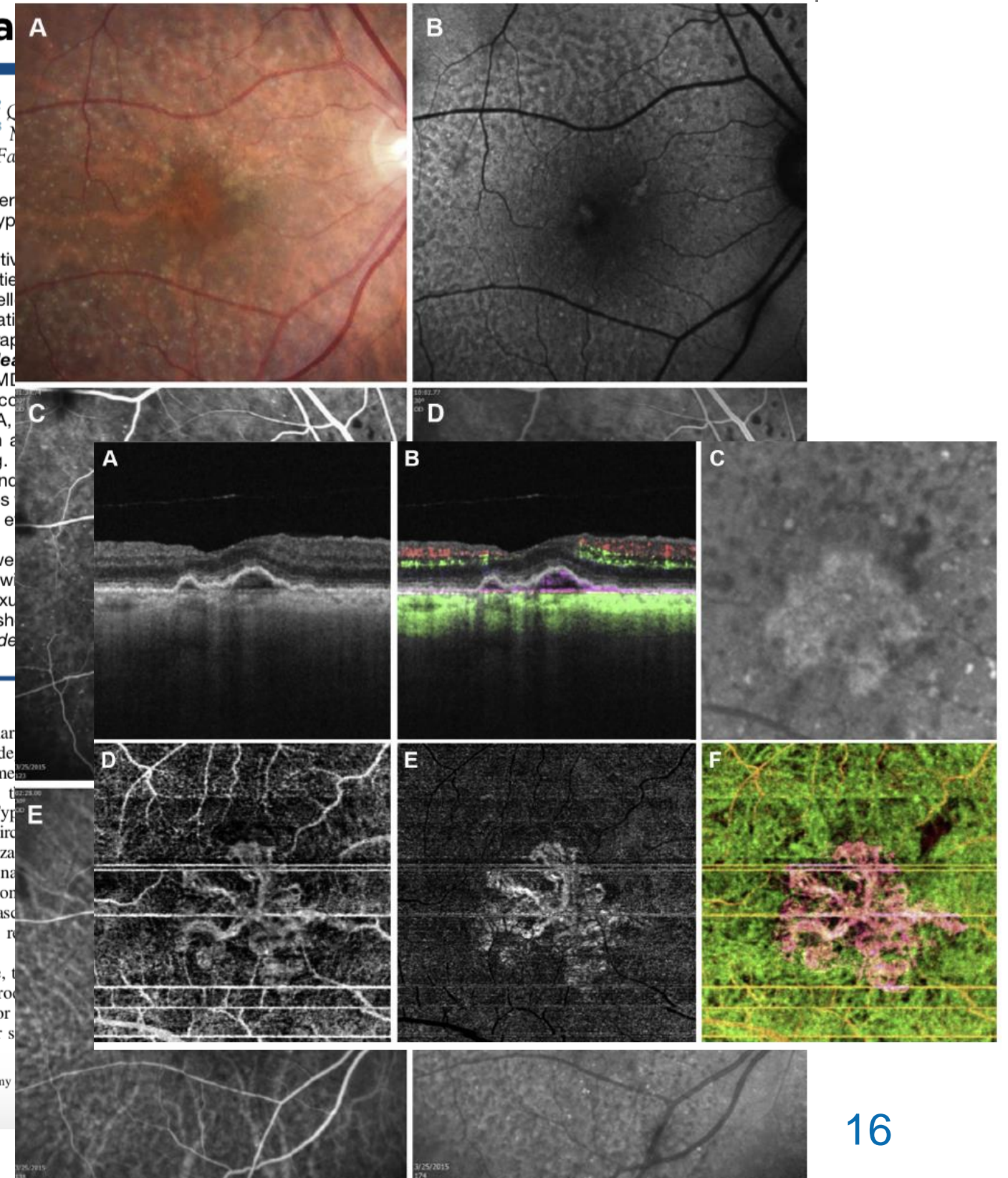
**Results:** Eleven eyes were imaged with FA, ICGA, and OCT. Seven eyes revealed drusen and fluorescein leakage. In 11 asymptomatic eyes, OCT angiography identified neovascularization to the plaques in all 3 eyes, and in 8 eyes.

**Conclusions:** Swept-source OCT angiography in asymptomatic eyes with intermediate AMD identifies neovascularization to the plaques, a system that distinguishes it from the American Academy of Ophthalmology.

The onset of macular age-related macular degeneration (AMD) progression from intermediate AMD to exudative AMD, and the division into 3 types. Type 1 neovascularization from the choroidal circulation exists beneath the Retinal Pigmented Epithelium (RPE). Type 2 neovascularization exists beneath the RPE. Type 3 neovascularization exists beneath the RPE and is also associated with proliferation.

Over the past decade, the treatment of AMD has been revolutionized by the introduction of anti-vascular endothelial growth factor (VEGF) therapy. It is initiated after the identification of neovascularization.

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# Summary

- APL-2 inhibits C3 and the downstream effects of the complement cascade
- APL-2 when given monthly or every other month demonstrated statistically significant differences in GA growth over 18 months as compared to placebo patients despite no treatment for 6 months
- APL-2 slowed growth of GA independent of Complement Factor I genotype
- Upon discontinuation of APL-2 at month 12, the treatment effect declines
- The risk/benefit profile at 18 months supports the decision to move to Phase 3 testing