A Prospective, Single-Blind, Randomized Study to Evaluate Intravitreal Aflibercept Injection versus Sham as PROphylaxis against CONversion to Neovascular Age-Related Macular Degeneration in High-Risk Eyes

The PRO-CON Study

Month 24 Results

Sumit P. Shah, MD

Jeffrey Heier, MD
Sabin Dang, MD

David Brown, MD
Nadia Waheed, MD

David Boyer, MD
Namrata Saroj, OD

PRO-CON Study Investigators
Financial Disclosures

- Jeffrey Heier, David Boyer, David Brown
  - Consultants: Regeneron, Genentech, Novartis, Optovue
- Nadia Waheed
  - Director, Boston Imaging Reading Center
- Sabin Dang, Sumit Shah
  - No relevant financial disclosures

- PROCON is an Investigator-sponsored trial (IST) supported by Regeneron. Study design, implementation and analysis performed by investigators.

Summary

- Aflibercept quarterly prophylaxis did not affect conversion through Month 24
- Exudative disease in fellow eye ≤ 2 years had a higher conversion rate
- Presence of non-exudative CNV confirmed on OCTA was more likely to convert in either group
- Development or progression of geographic atrophy was not affected by quarterly aflibercept treatment

Rates of CNV Conversion in Fellow Eyes at 24 Months

Comparison of Spectral Domain OCT (SD-OCT) and Fluorescein Angiography (FA) Conversion Rates in Fellow Eyes of HARBOR Patients

Intravitreal Aflibercept Injection for Neovascular Age-related Macular Degeneration

Ninety-Six–Week Results of the VIEW Studies

Ursula Schmidt-Erfurth, MD,[1] Peter K. Kaiser, MD,[2] Jean-François Korobelnik, MD,[3] David M. Brown, MD,[4] Victor Chong, MD,[5] Quan Dong Nguyen, MD,[6] Allen C. Ho, MD,[7] Yuichiro Ogura, MD,[8] Christian Simader, MD,[1] Glenn J. Jaffe, MD,[9] Jason S. Slakter, MD,[10] George D. Yancopoulos, MD, PhD,[11] Neil Stahl, PhD,[11] Robert Vitti, MD,[11] Alyson J. Berliner, MD, PhD,[11] Yuhwen Soo, PhD,[11] Majid Anderesi, MD,[12] Olaf Strauble, MD,[12] Oliver Zeitz, MD,[12,13] Christiane Nowenberg, MS,[12] Rupert Sandbrink, MD, PhD,[12,14] Jeffrey S. Heier, MD[15]

Purpose: To determine efficacy and safety of intravitreal aflibercept in patients with neovascular age-related macular degeneration (AMD) during a second year of variable dosing after a first-year fixed-dosing period.

Design: Two randomized, double-masked, active-controlled, phase 3 trials.

Participants: Two thousand four hundred fifty-seven patients with neovascular AMD.

Methods: From baseline to week 52, patients received 0.5 mg intravitreal ranibizumab every 4 weeks (Rq4), 2 mg aflibercept every 4 weeks (2q4), 0.5 mg aflibercept every 4 weeks (0.5q4), or 2 mg aflibercept every 8 weeks (2q8) after 3 monthly injections. During weeks 52 through 96, patients received their original dosing assignment using an as-needed regimen with defined retreatment criteria and mandatory dosing at least every 12 weeks.

Main Outcome Measures: Proportion of eyes at week 96 that maintained best-corrected visual acuity (BCVA; lost <15 letters from baseline); change from baseline in BCVA.

Results: Proportions of eyes maintaining BCVA across treatments were 94.4% to 96.1% at week 52 and 91.5% to 92.4% at week 96. Mean BCVA gains were 8.3 to 9.3 letters at week 52 and 6.6 to 7.9 letters at week 96. Proportions of eyes without retinal fluid decreased from week 52 (60.3% to 72.4%) to week 96 (44.6% to 54.4%), and more 2q4 eyes were without fluid at weeks 52 and 96 than Rq4 eyes (difference of 10.4% [95% confidence interval {CI}, 4.9–15.9] and 9.0% [95% CI, 3.0–15.1]). Patients received on average 16.5, 16.0, 16.2, and 11.2 injections over 96 weeks and 4.7, 4.1, 4.6, and 4.2 injections during weeks 52 through 96 in the Rq4, 2q4, 0.5q4, and 2q8 groups, respectively. The number of injections during weeks 52 through 96 was lower in the 2q4 and 2q8 groups versus the Rq4 group (differences of −0.64 [95% CI, −0.89 to −0.40] and −0.55 [95% CI, −0.79 to −0.30]; $P < 0.0001$, post hoc analysis). Incidences of Antiplatelet Trialists' Collaboration–defined arterial thromboembolic events were similar across groups (2.4% to 3.8%) from baseline to week 96.

Conclusions: All aflibercept and ranibizumab groups were equally effective in improving BCVA and preventing BCVA loss at 96 weeks. The 2q8 aflibercept group was similar to ranibizumab in visual acuity outcomes during 96 weeks, but with an average of 5 fewer injections. Small losses at 96 weeks in the visual and anatomic gains seen at 52 weeks in all arms were in the range of losses commonly observed with variable dosing. *Ophthalmology 2014;121:193-201*

- **MARINA/ ANCHOR** — **24-38%**
- **CATT** — **17-21%**
- **HARBOR (M 12)** — **12% (FA) 50% *(SD-OCT)***
- **VIEW** — **26-32%**

Study Objective

To evaluate if intravitreal anti-VEGF therapy in eyes with high-risk dry AMD would provide a prophylactic effect against the conversion to nAMD

Study Design

- **128* eyes with high risk dry AMD randomized 1:1 to quarterly treatments** with:
  - Intravitreal aflibercept injection (IAI)
  - Sham Injection

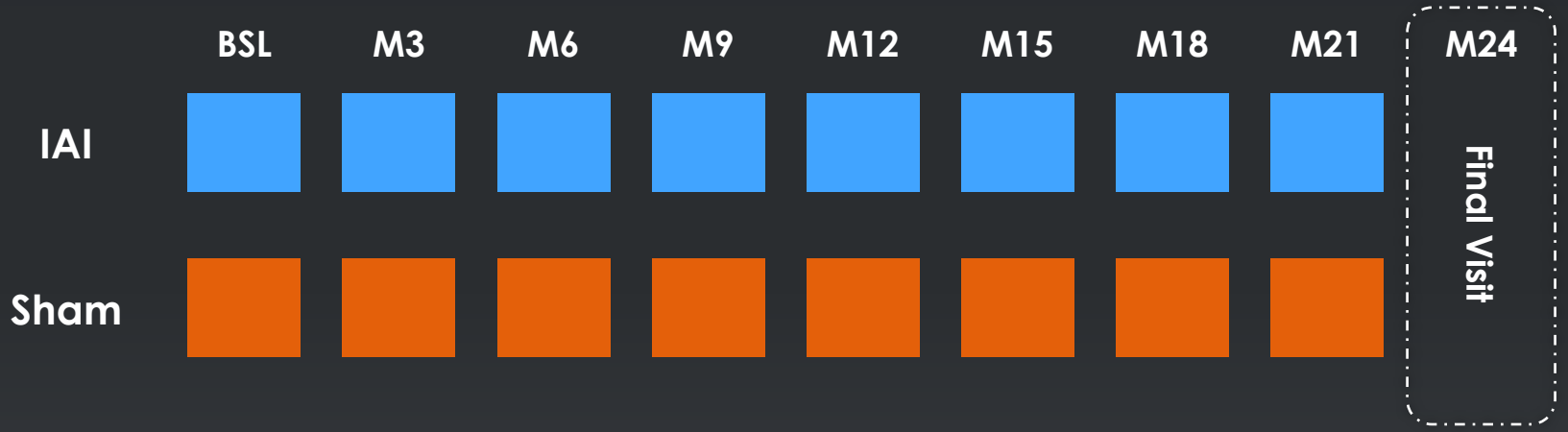
- **Study Duration: 24 months**
- Planned Interim Analysis: 12 months

- **Primary Endpoint:**
  - **Proportion of patients converting to nAMD at 24 months** characterized by CNV development as assessed by:
    - CNV leakage on FA, and
    - Evidence of any fluid on SD-OCT

    Conversion confirmed by masked, central reading center

**sample size based on 35% conversion rate at 2 years and 8% dropout/deaths annually*

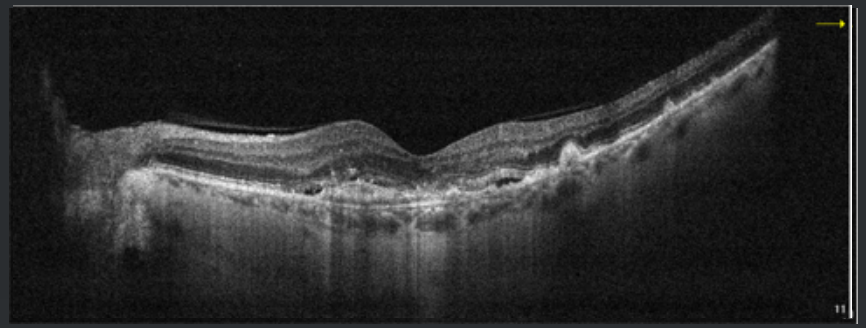
Study Schedule

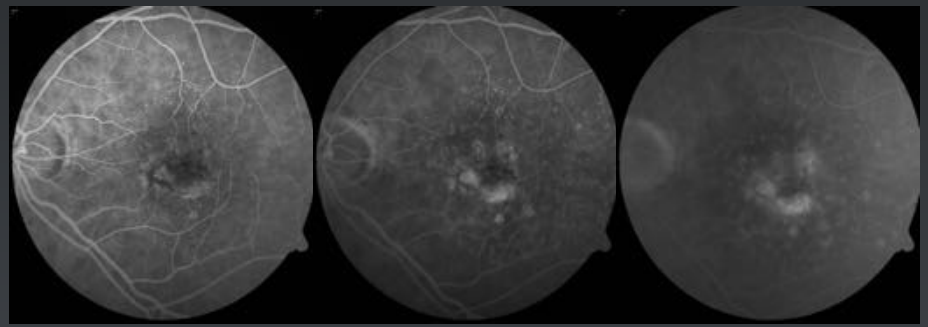


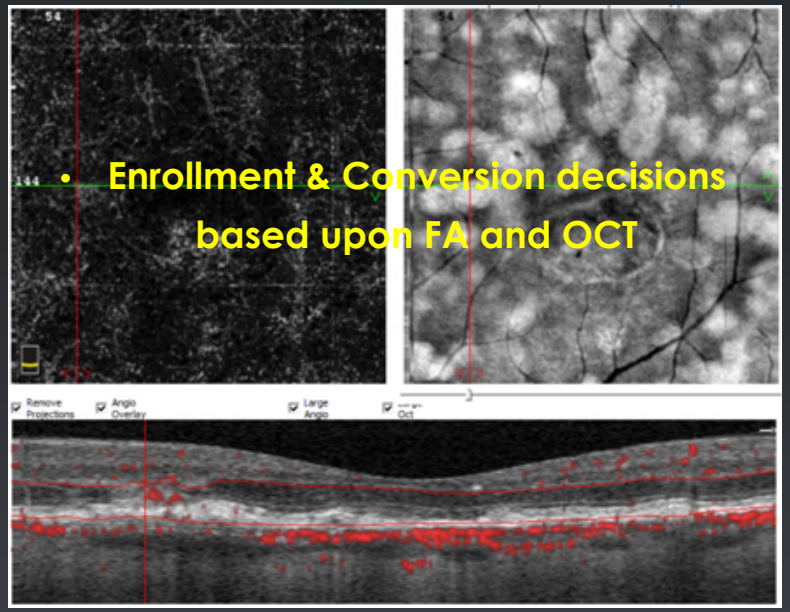
Assessments at all study visits *(including Unscheduled Suspected Conversion Visits)* -

- Best-Corrected Visual Acuity
- Spectral Domain-Optical Coherence Tomography
- Fluorescein Angiography
- Fundus Photos
- OCT-Angiography

Imaging at Every Visit

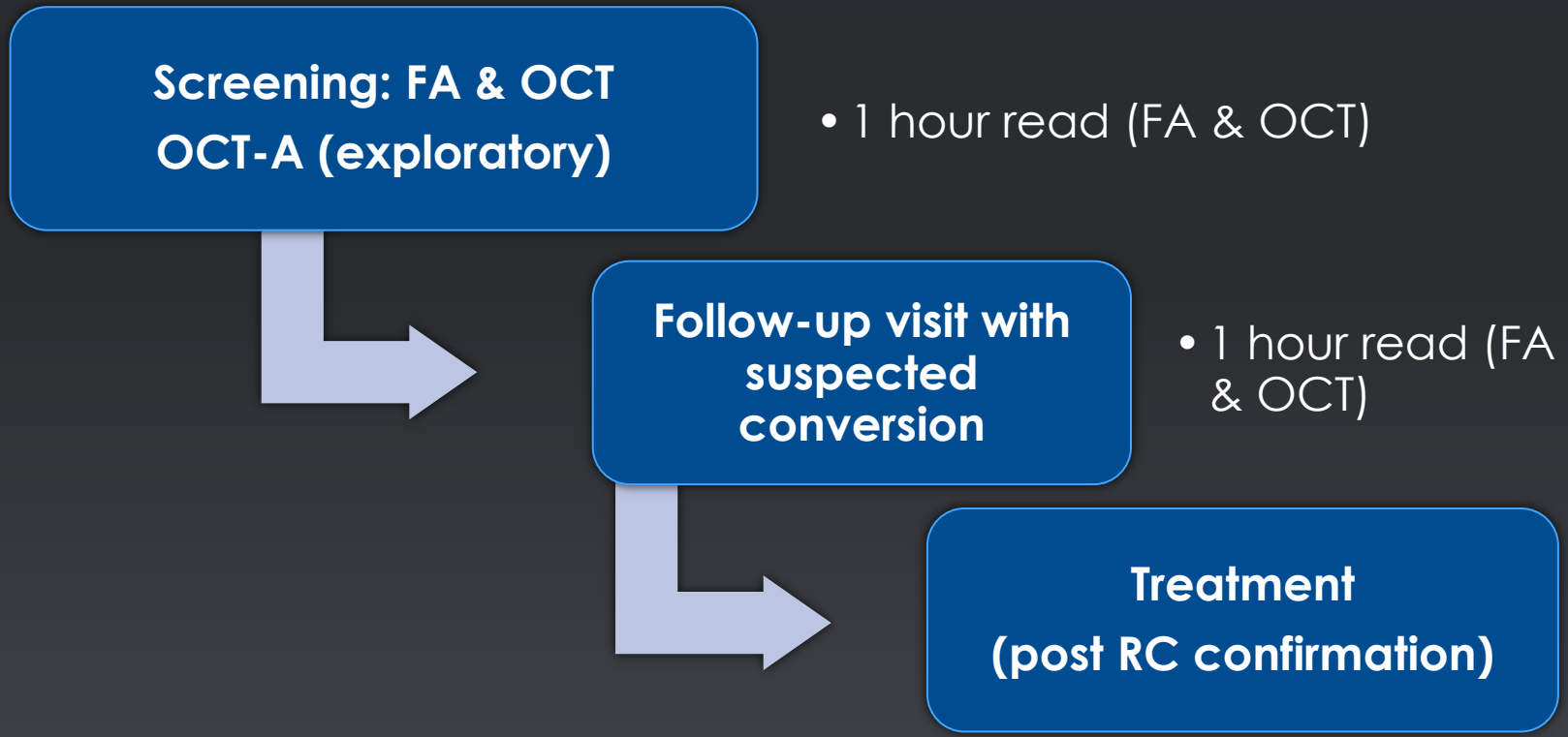






- Enrollment & Conversion decisions based upon FA and OCT

Mandatory Reading Center Confirmation
Boston Imaging Reading Center



Key Entry Criteria

- High risk defined as having
  - Intermediate AMD in one eye (study eye) defined as the presence of
    - > 10 intermediate sized drusen (≥ 63 and <125 µm)
    - ≥ 1 large druse (≥125 µm)
    - and/or retinal pigmentary changes

    and
  - Neovascular AMD in the fellow eye

- Absence of exudative disease confirmed by independent, masked reading center before enrollment

Baseline Characteristics

	IAI n = 63*	Sham n = 64
Age (years)	78.4	79.2
Female	27 / 63 (42.8%)	32 / 64 (50%)
Duration of fellow eye nvAMD ≤ 2y (%)	48%	48%
Non-Exudative Macular NV (OCTA)	6.3%	9.2%
Mean BCVA	78.7	77.3

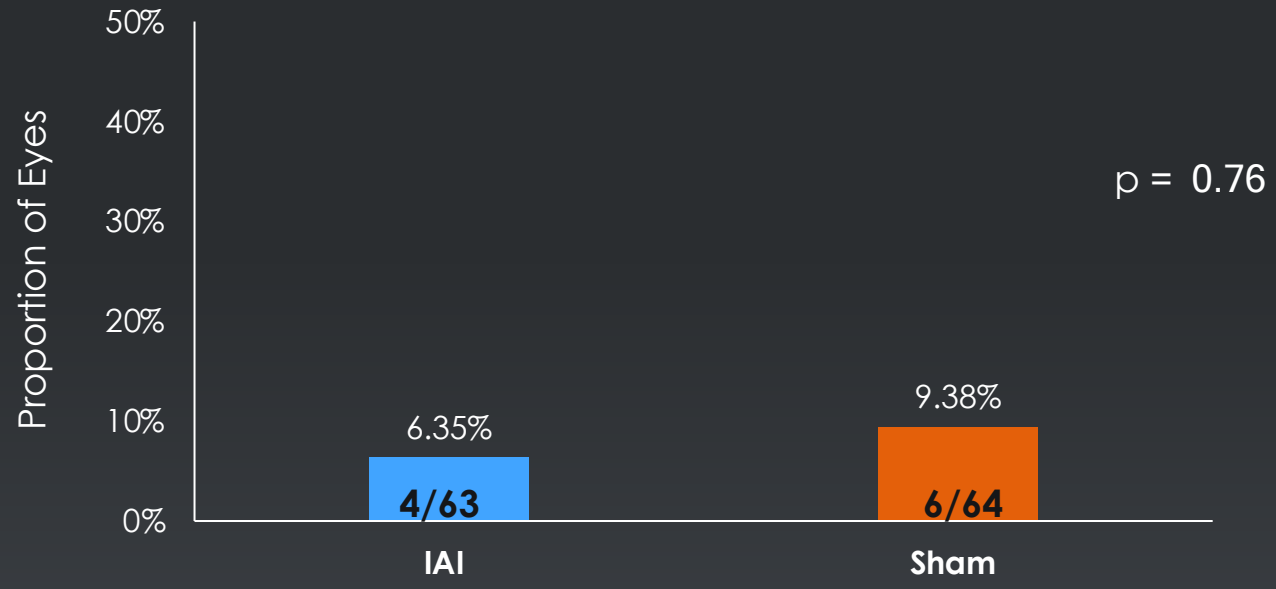
** 1 patient had exudative disease in the study eye at baseline*
*** As determined by OCT-A*

Patient Disposition

	IAI n = 64	**Sham n = 64**
Month 24, n (%)	60 (94%)	53 (83%)
Withdrew	3	6
Death	1	5

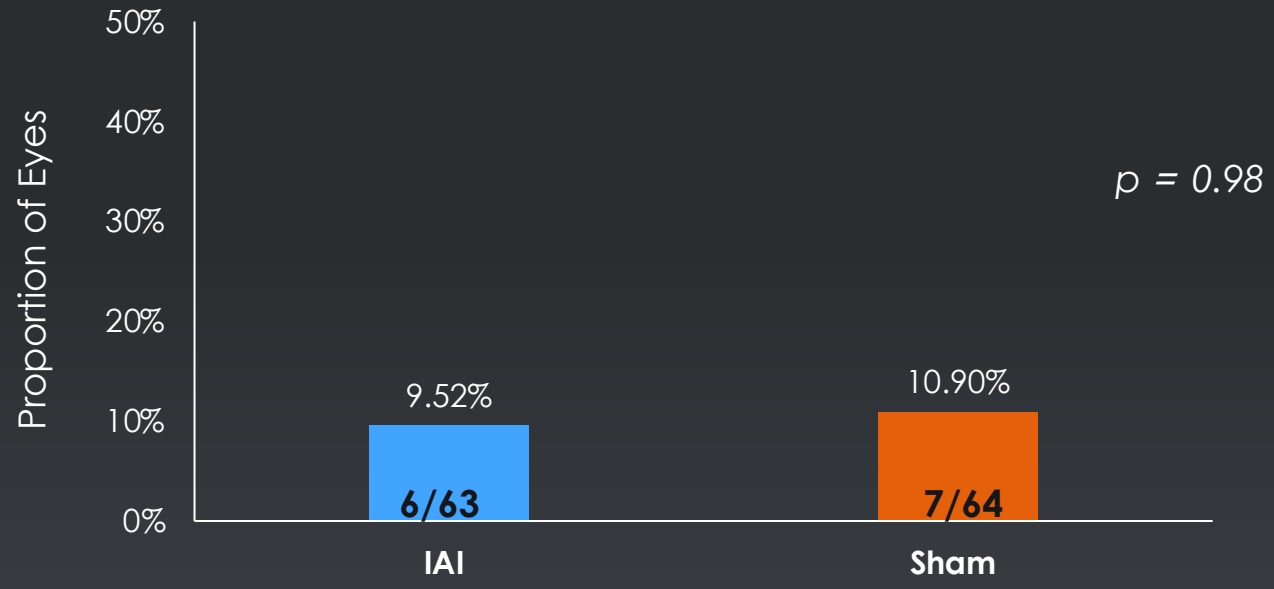
Month 12

Rate of CNV Conversion
Overall Population

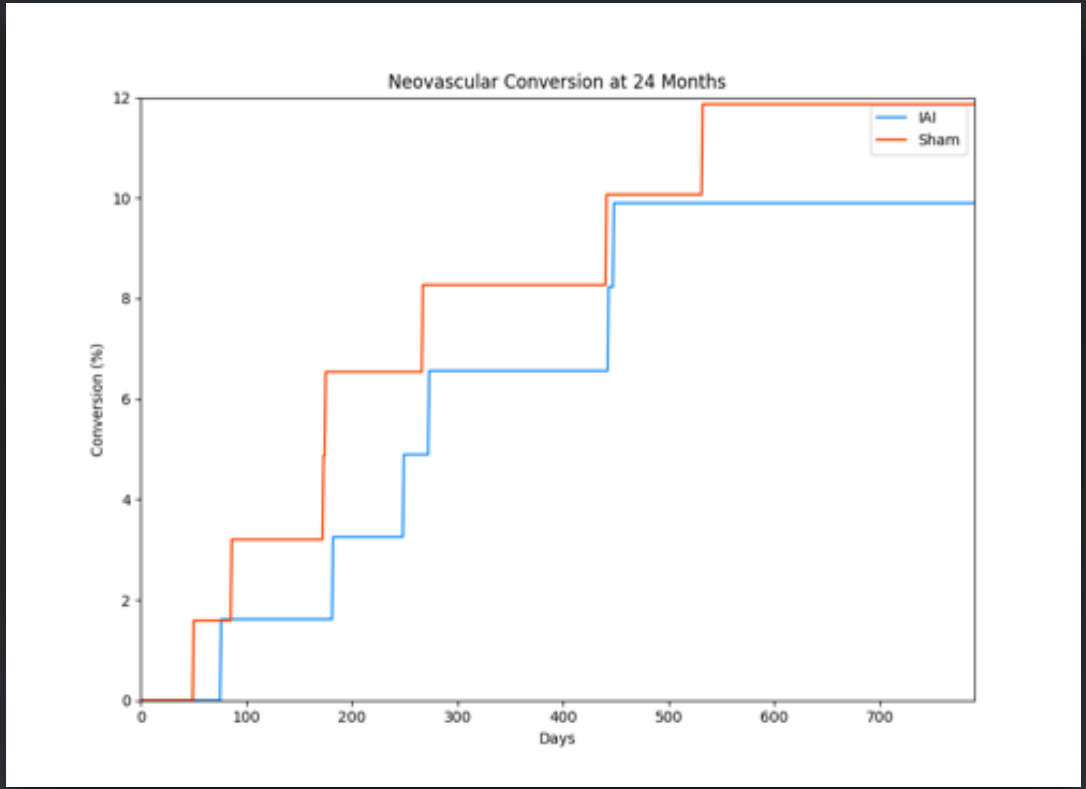


Month 24

Rate of CNV Conversion
Overall Population



Time to Conversion
Overall Population

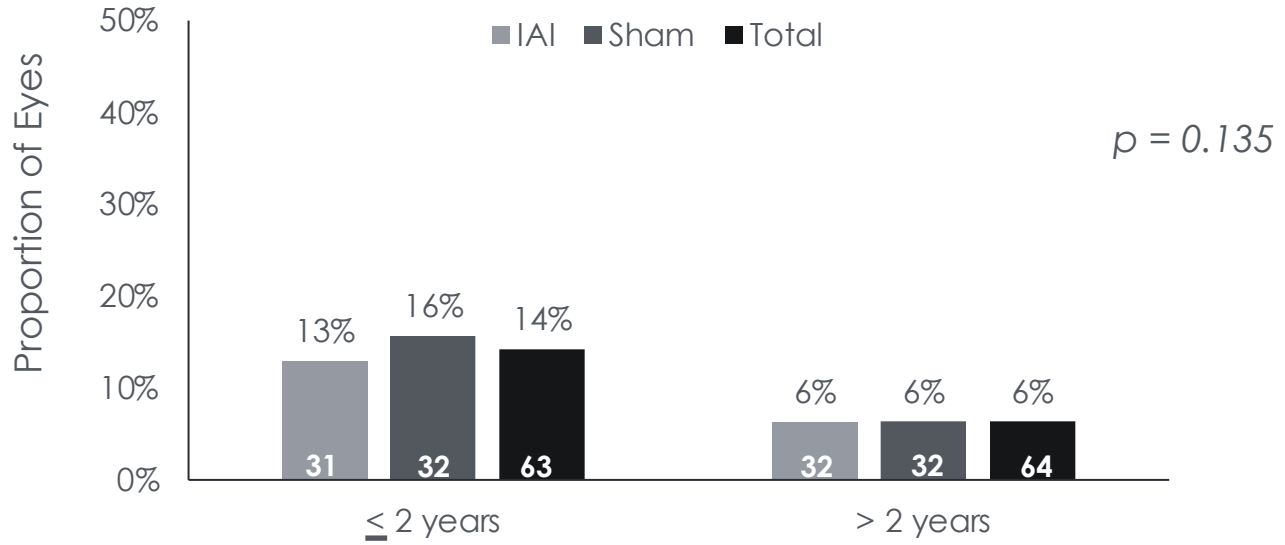


p=0.50

Month 24

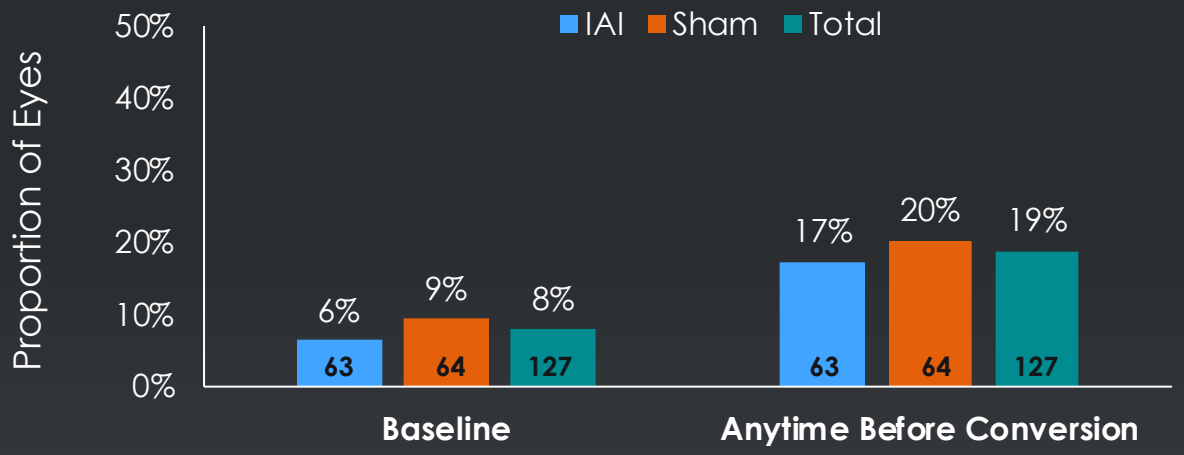
Rate of CNV Conversion

By Duration of Exudative Disease in the Fellow Eye



Month 24

Presence of Non-Exudative Choroidal Neovascularization*



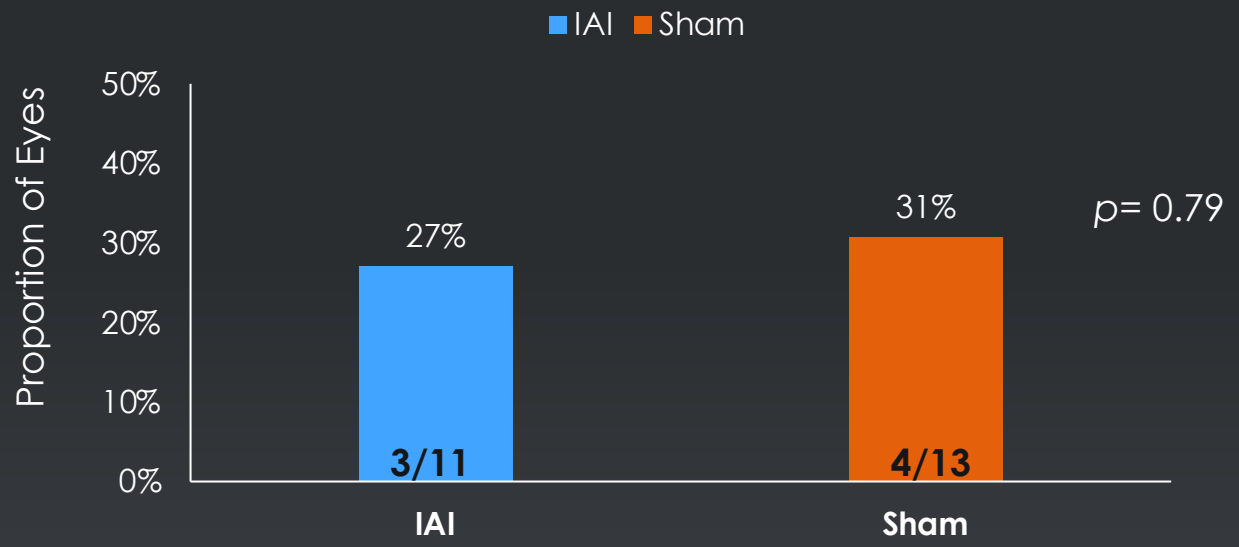
- ***Few patients developed NE-CNV during the 24-month period***

* As measured by OCT-A at any time during the trial before conversion

Month 24

Rate of CNV Conversion

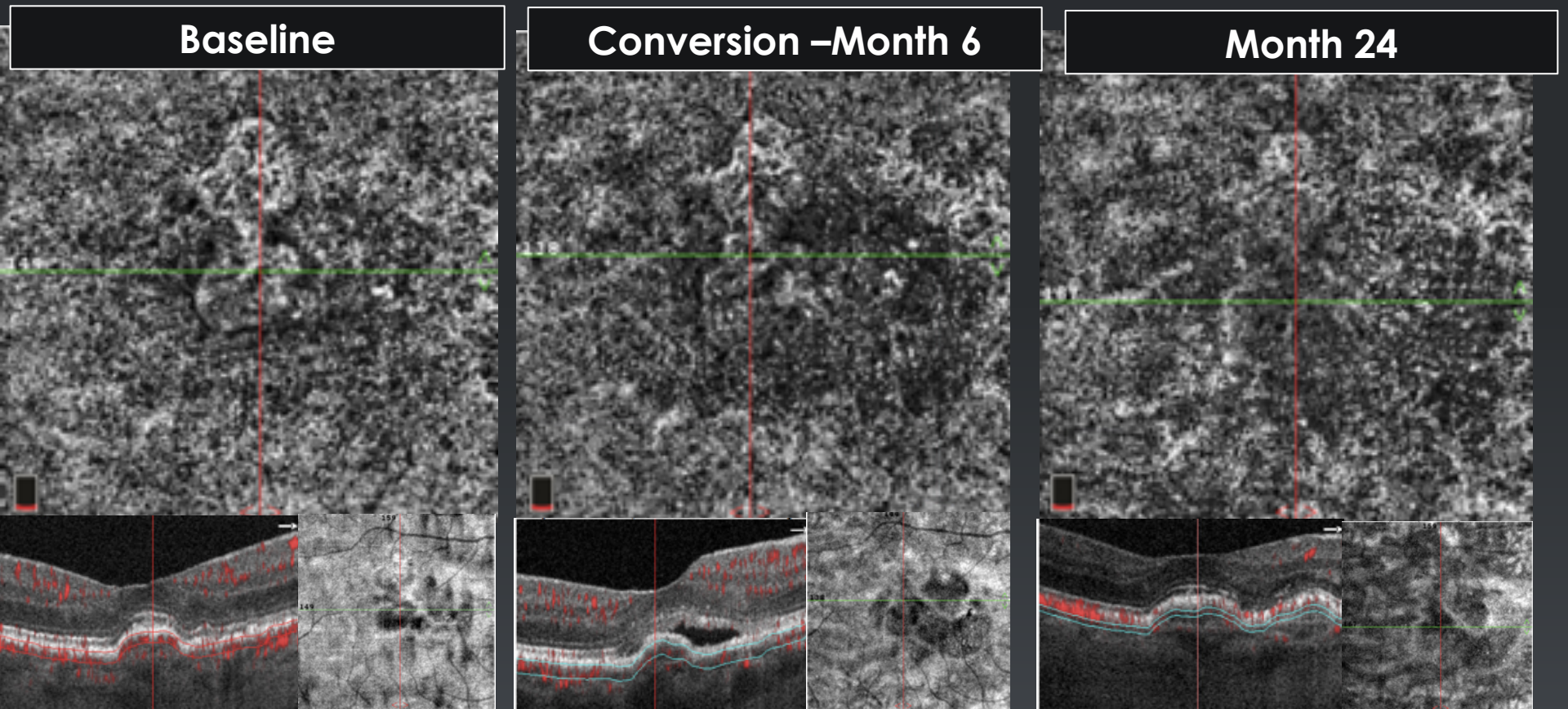
*In Eyes with Non-Exudative Choroidal Neovascularization**



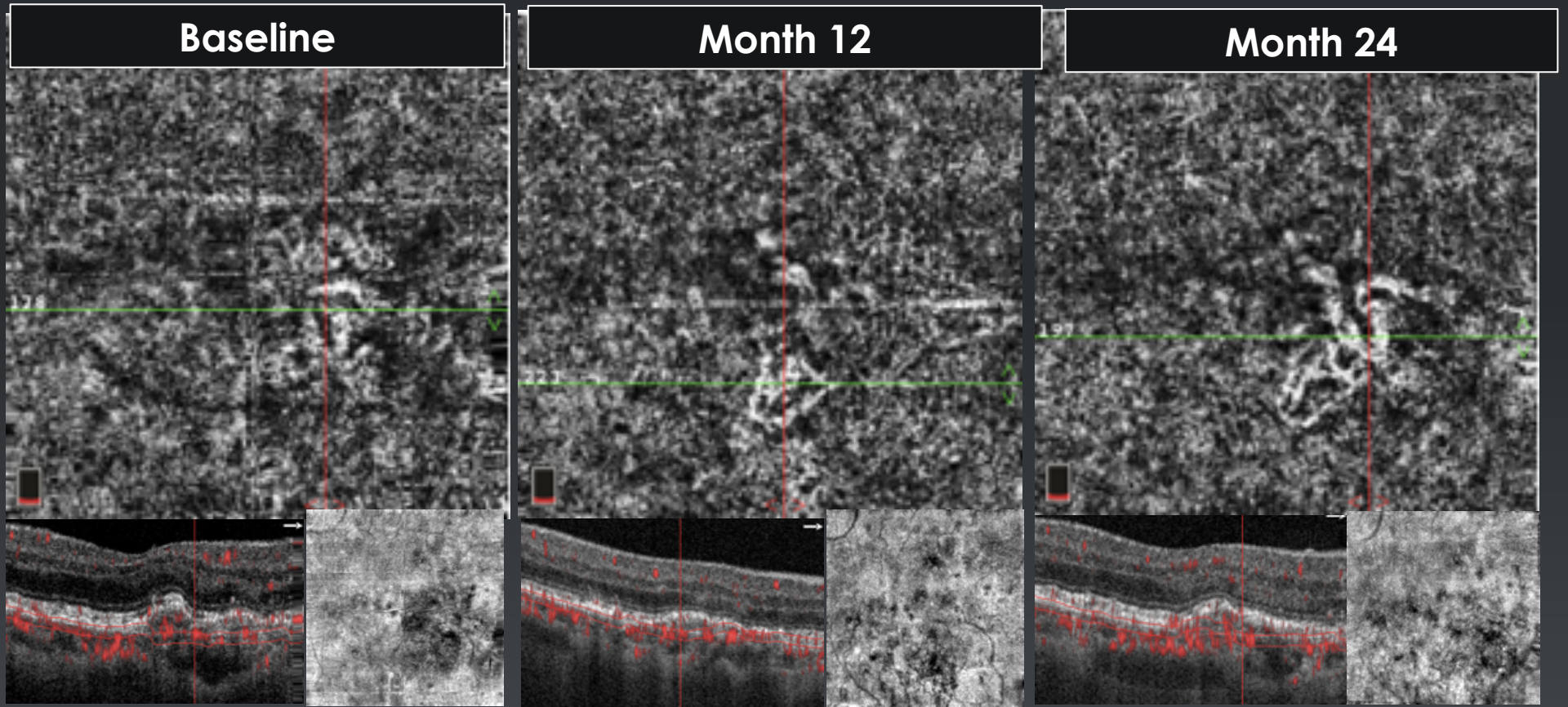
Patients with non exudative CNV had a higher conversion rate

* As measured by OCT-A at any time during the trial before conversion

Non-exudative CNV at Baseline with Conversion



Non-exudative CNV at Baseline without Conversion



Safety

- One related, significant ocular adverse event reported by M24
  - Endophthalmitis in fellow eye related to injection procedure
- Safety data were consistent with previous studies involving intravitreal injections

Conclusions

- Aflibercept quarterly prophylaxis did not affect conversion through Month 24
- Exudative disease in fellow eye ≤ 2 years had a higher conversion rate
- Presence of non-exudative CNV confirmed on OCTA was more likely to convert in either group
- Development or progression of geographic atrophy was not affected by quarterly aflibercept treatment

Thank you to study sites, BIRC, consultants, patients

- **David Boyer, MD**
  - RVA, Los Angeles
- **David Brown, MD**
  - Houston Retina
- **Sumit Shah, MD**
  - New Jersey Retina
- **Jeffrey S. Heier, MD**
  - OCB(Coordinating Center)
- **Nadia Waheed, MD (Chair)**
- **Yasin Alibhai**
  - BIRC
- **Sabin Dang, MD**
  - Retina Institute, St. Louis
- **Namrata Saroj, OD**
  - Consultant