AMD Clinical Trial Design after recent Draft FDA Guidance

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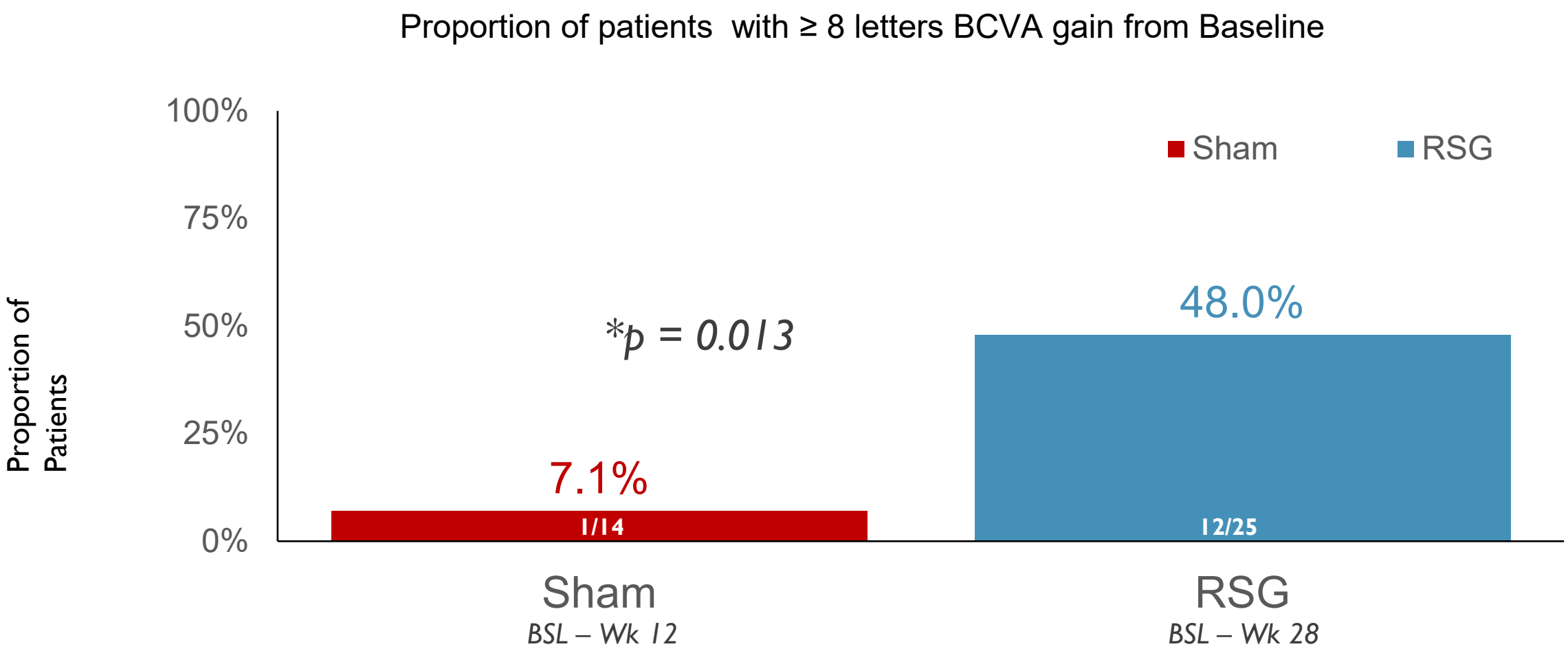
All conflict of interest reviewed and approved by the Cleveland Clinic Conflict of Interest Committee

FDA Endpoints in dry AMD

- Superiority:
    - FDA requires ≥ 15 ETDRS letter improvement or prevention of worsening

Risuteganib Phase 2a: Primary Endpoint

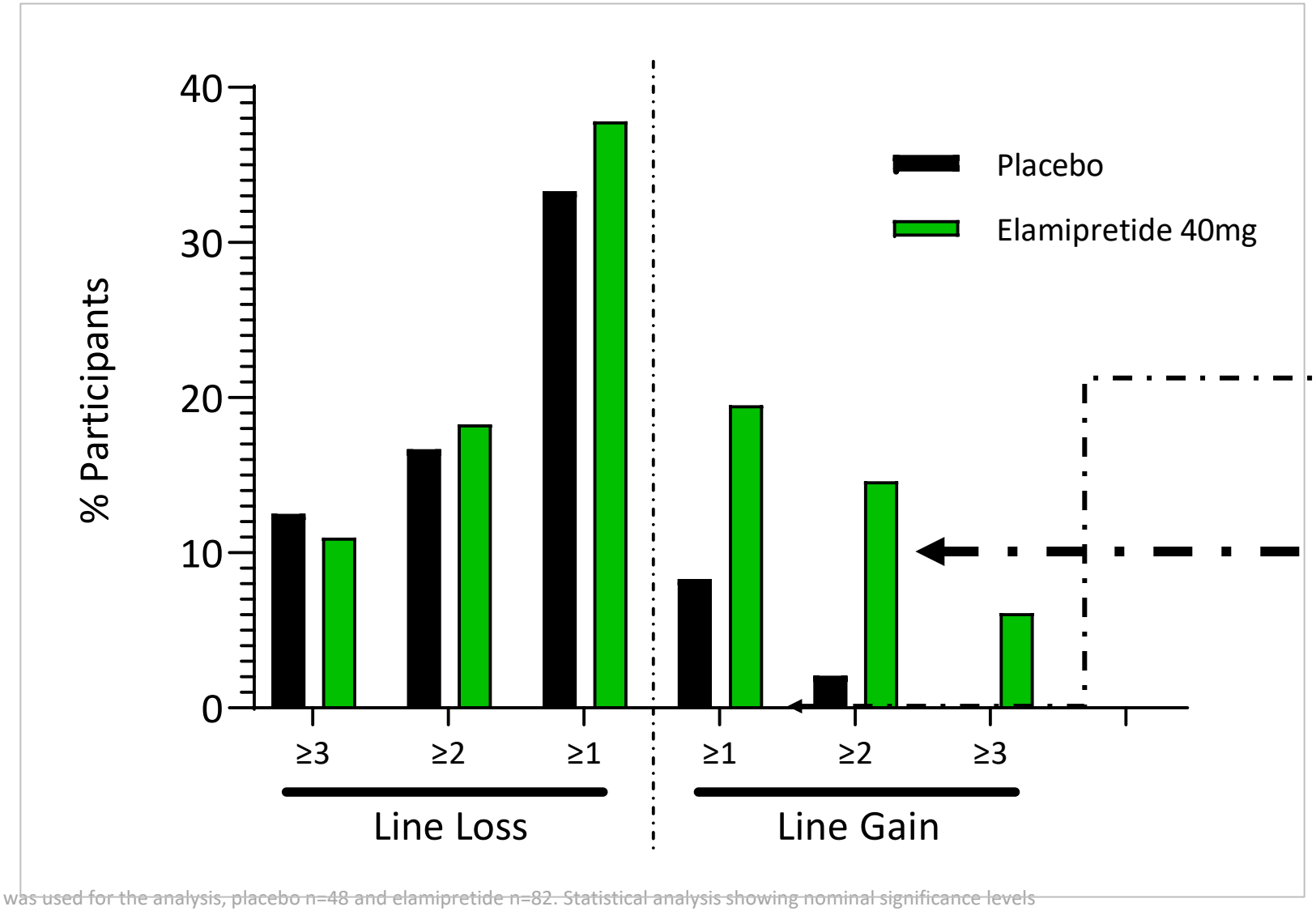


Per Protocol Population

Kaiser PK Euretina 2019 Paper Presentation

ReCLAIM-2 Demonstrated Categorical LLVA Improvement

No other investigational product has demonstrated the potential to improve LLVA in patients with GA secondary to dry AMD

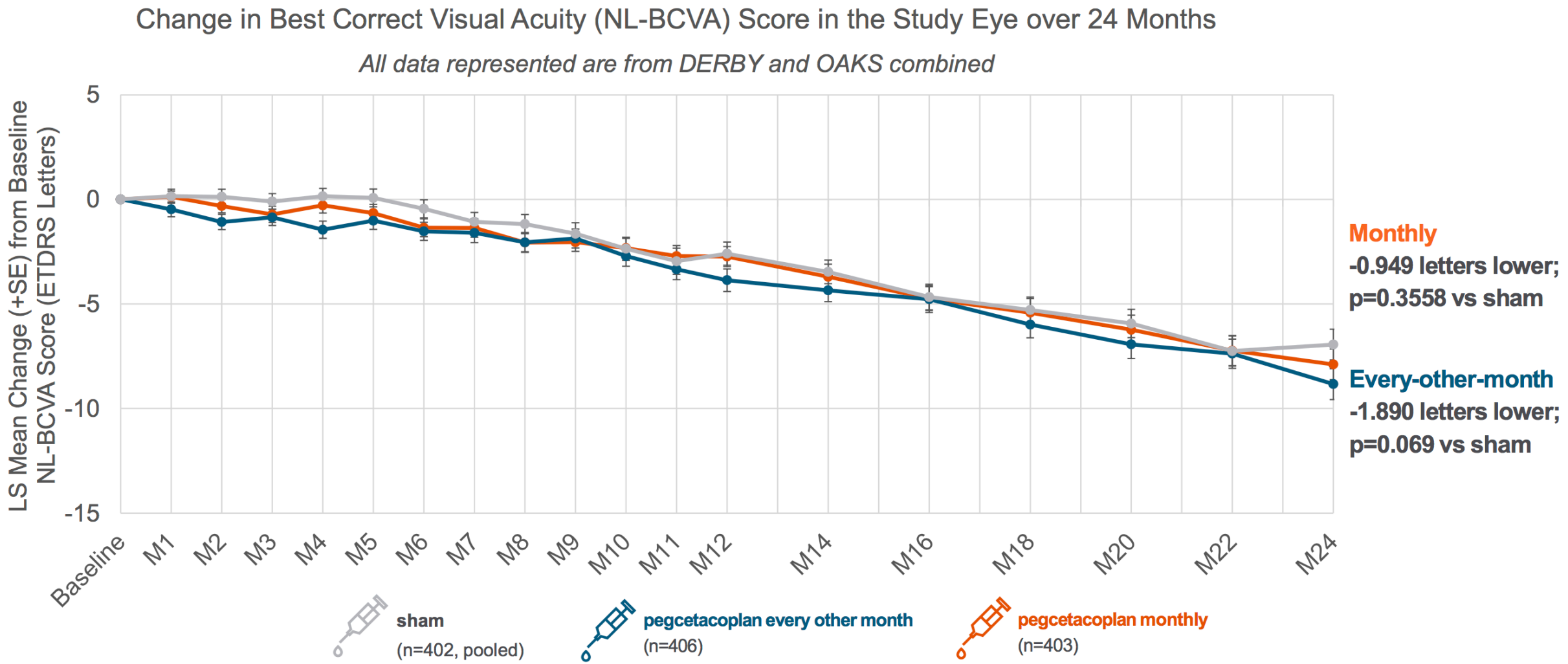


8+ Letter Gain:
Elam: 17% (n=14)
Placebo: 4% (n=2)
P<0.05

≥2 Line Gain:
Elam: n=12 @ 2 lines
Elam: n=5 @ 3 lines
P=0.04

The mITT population was used for the analysis, placebo n=48 and elamipretide n=82. Statistical analysis showing nominal significance levels

No clinically meaningful or statistically significant differences were observed in key functional endpoints



GA=geographic atrophy; SE= standard error. Least square (LS) means estimated from a mixed-effects model for repeated measures (MMRM). The mITT population was used for the analysis, defined as all randomized patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least one post-baseline value of GA lesion area in the study eye.

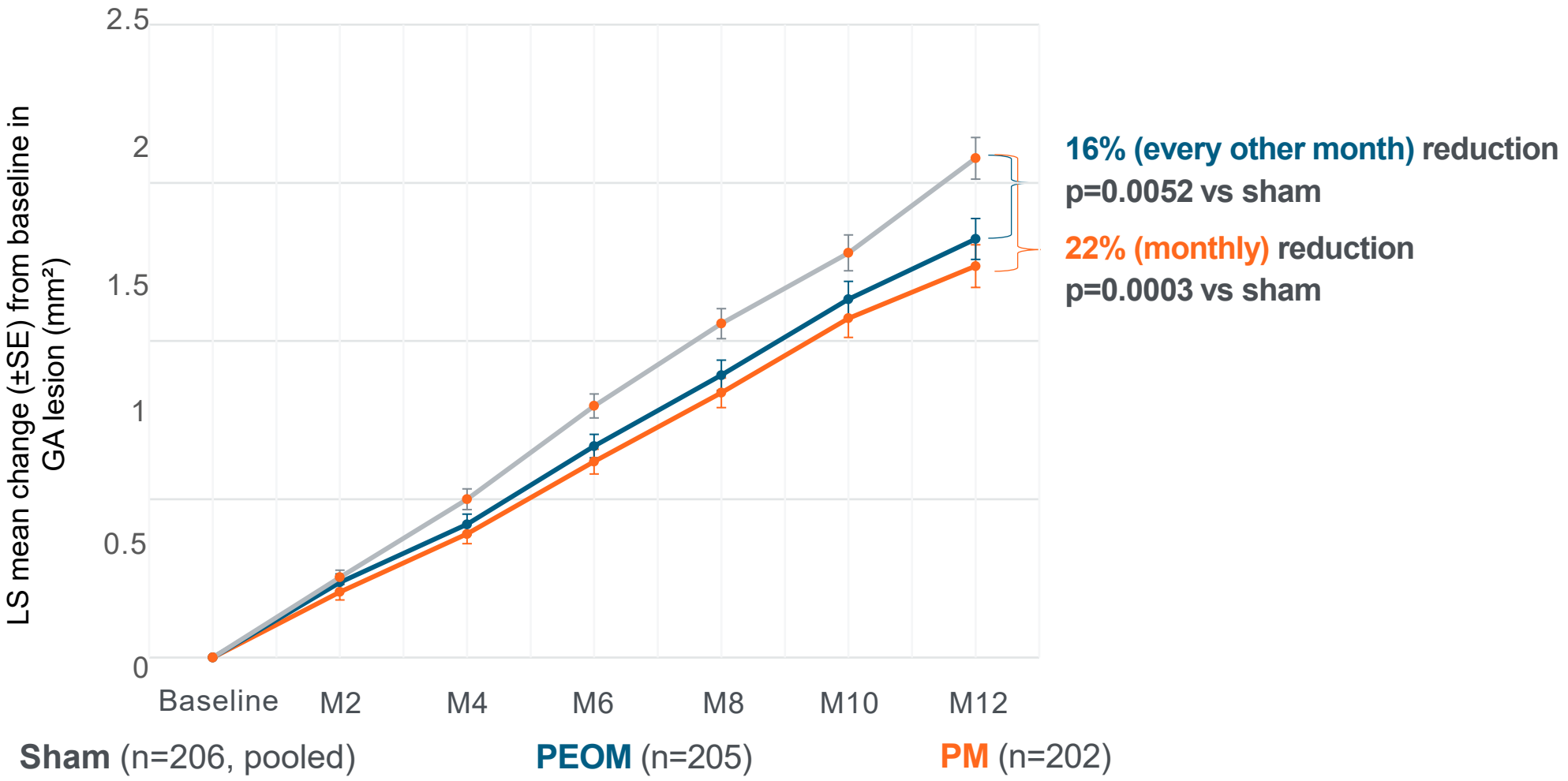
FDA Endpoints in dry AMD

- Superiority:
    - FDA requires ≥ 15 ETDRS letter improvement or prevention of worsening
- Accepted Surrogate Endpoints:
    - Prevention of Photoreceptor loss
        - Ellipsoid Zone (EZ) changes precede RPE loss

FDA Endpoints in dry AMD

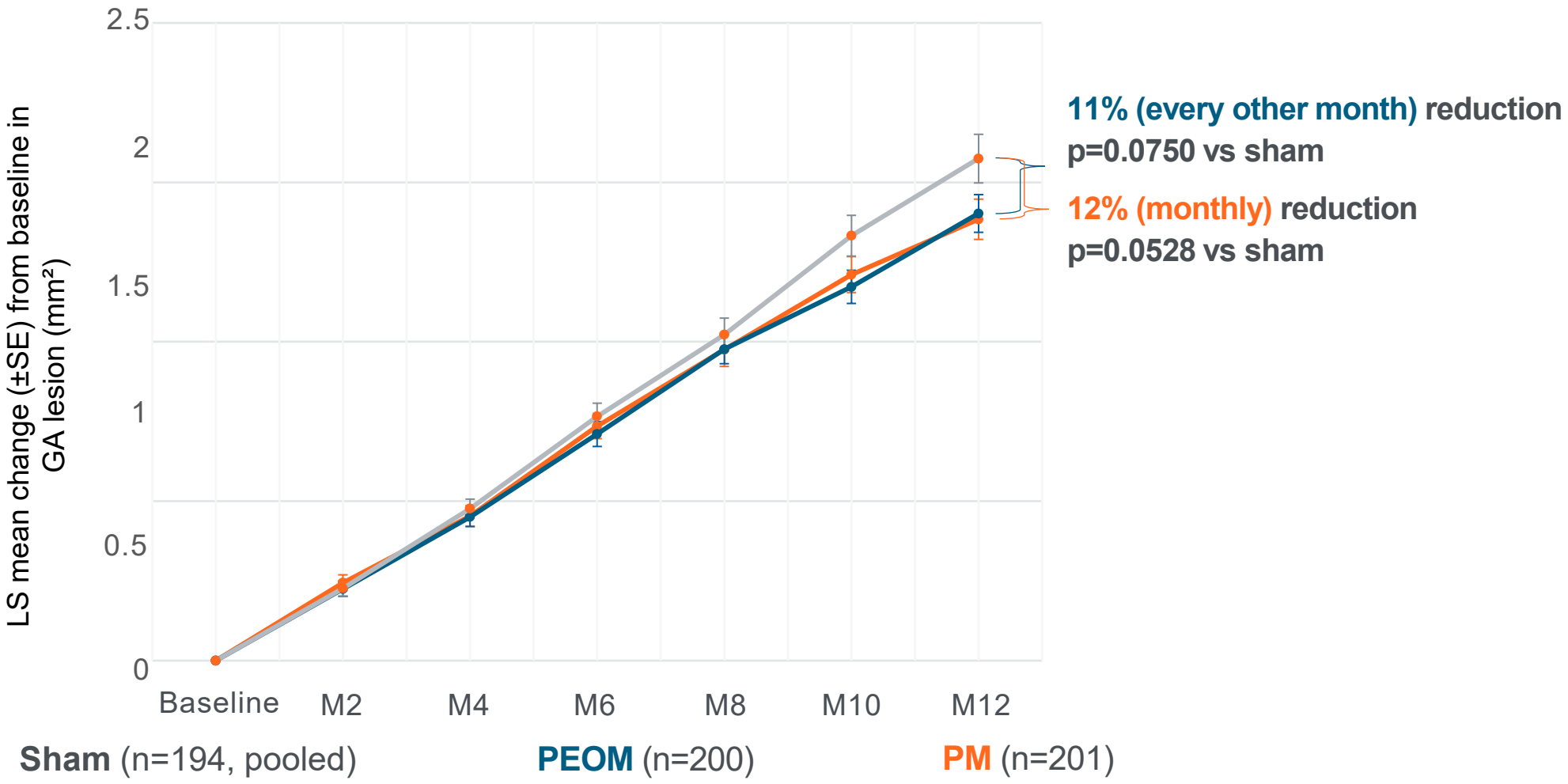
- Superiority:
  - FDA requires ≥ 15 ETDRS letter improvement or prevention of worsening
- Accepted Surrogate Endpoints:
  - Prevention of Photoreceptor loss
    - Ellipsoid Zone (EZ) changes precede RPE loss
    - Prevention of RPE loss

Pegcetacoplan monthly and every other month met the primary endpoint in **OAKS**



LS means estimated from a mixed-effects model for repeated measures (MMRM). The modified intention-to-treat population was used for the analysis, defined as all randomized patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least 1 post-baseline value of GA lesion area in the study eye.
GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

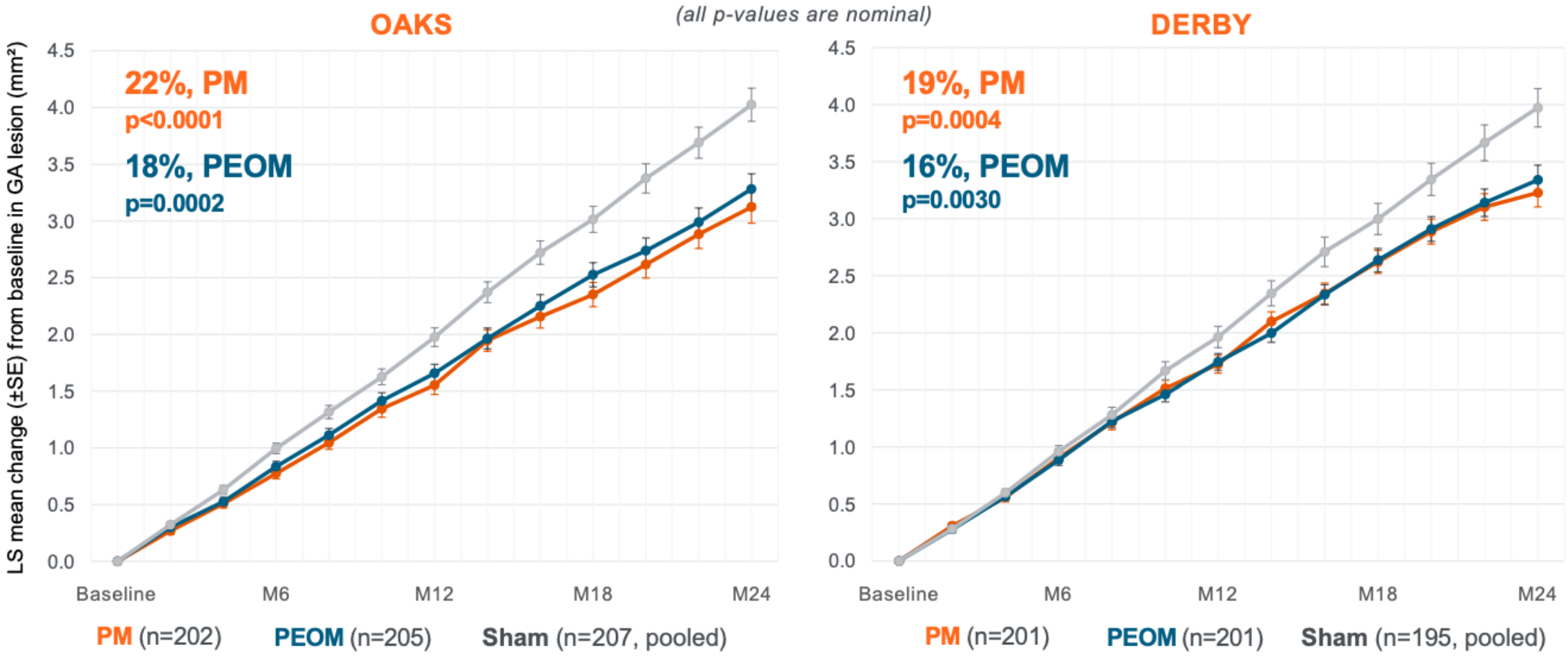
Pegcetacoplan did not meet the primary endpoint in **DERBY**



LS means estimated from a mixed-effects model for repeated measures. The modified intention-to-treat population was used for the analysis.
GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

Reductions in GA lesion growth at Month 24

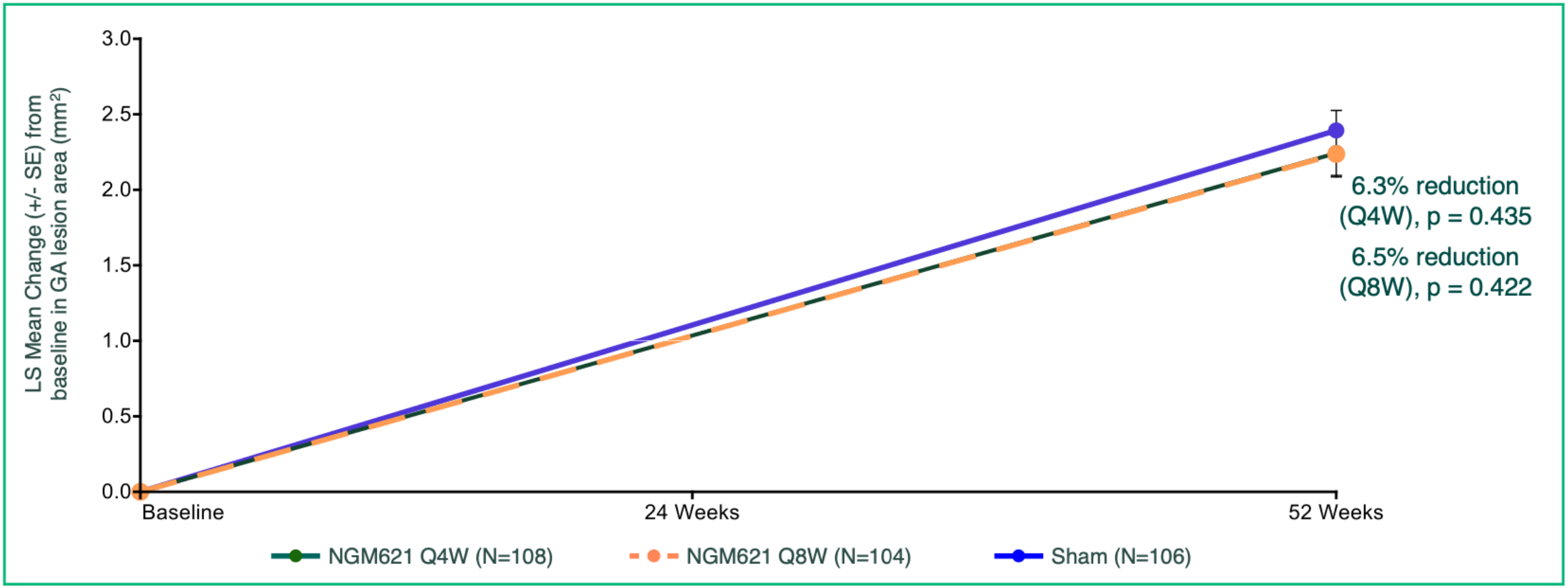
(all p-values are nominal)



LS means estimated from MMRM analysis. The mITT population was used for the analysis, defined as all randomized patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least one post-baseline value of GA lesion area in the study eye.
GA=geographic atrophy; LS=least square; M=month; mITT=modified intent-to-treat; MMRM=mixed-effects model for repeated measures; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

NGM Phase 2 - Primary Endpoint

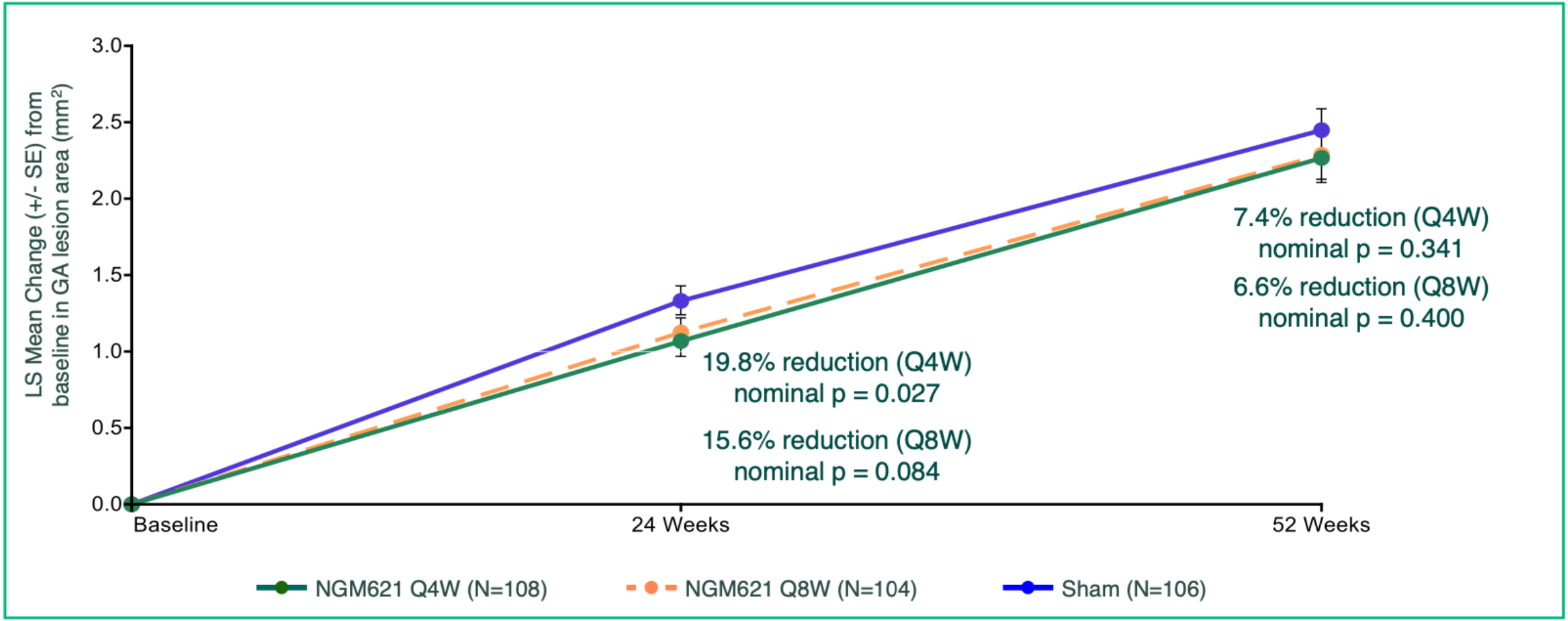
Rate of Change (Slope Analysis) in GA Lesion Area over 52 Weeks



Slope is generated from all available timepoints (Baseline, 24 weeks, 52 weeks)
The Least Square (LS) mean is estimated from a random coefficients linear growth model
The mITT analysis set includes all randomized and treated (with at least one study treatment) patients SE = standard error

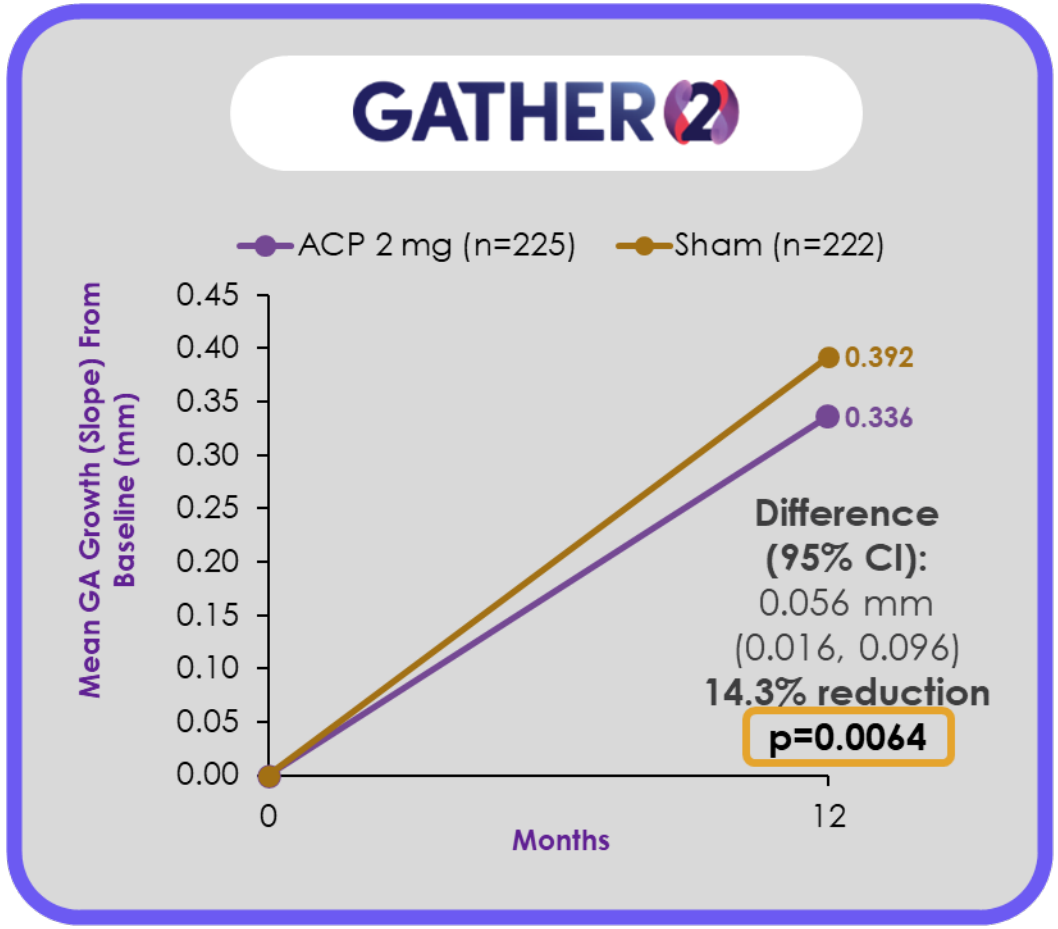
NGM Phase 2 - Secondary Analysis (MMRM)

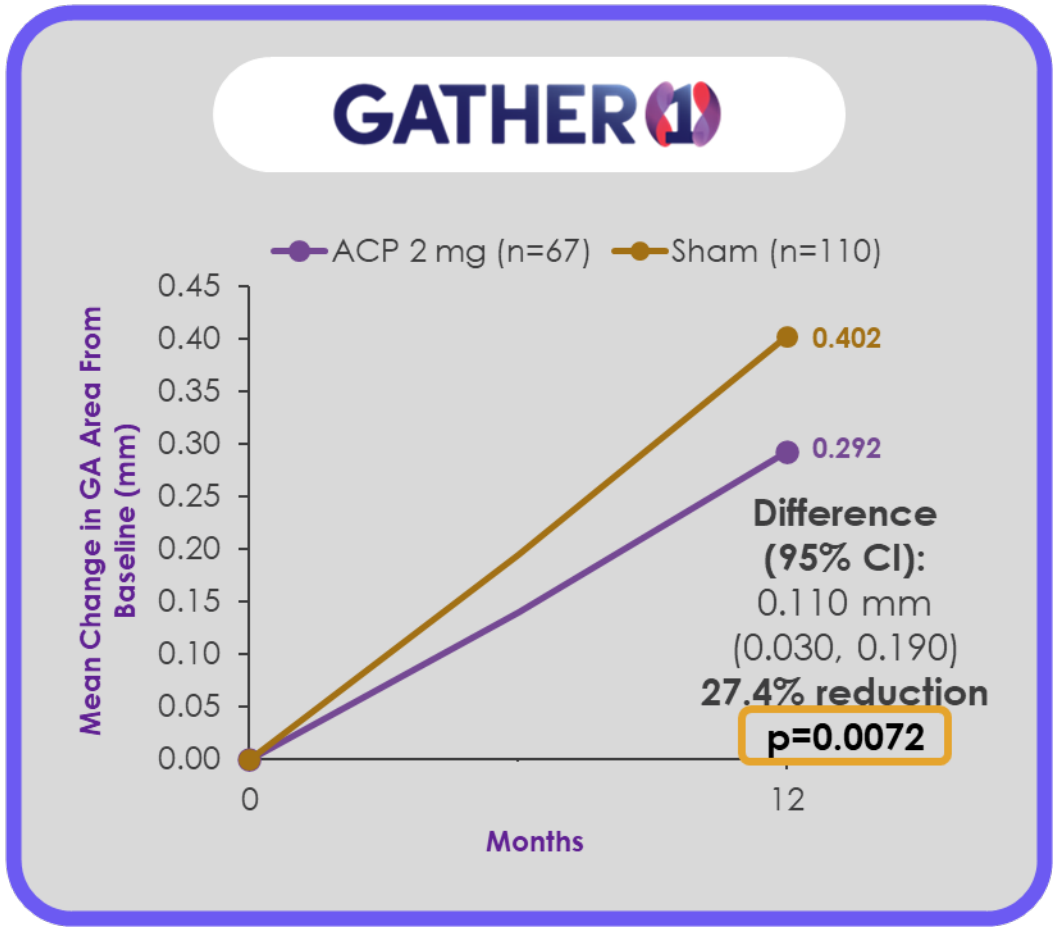
Change from Baseline in GA Lesion Area (MMRM) over 52 Weeks



The Least Square (LS) means is estimated from a mixed model for repeated measures (MMRM)
The mITT analysis set includes all randomized and treated (with at least one study treatment) patients

Avacincaptad pegol achieved the 12-month prespecified, primary endpoint, in two pivotal, phase 3 studies[1,2]





ACP, avacincaptad pegol; CI, confidence interval; GA, geographic atrophy.

1. Khanani AM, et al. Presented at: Retina Society; November 2-5, 2022; Pasadena, CA; 2. Jaffe GJ, et al. *Ophthalmology*. 2021;128:576-586.

Practical Considerations

- Currently, therapies targeting early or intermediate dry AMD have no practical path forward
- Only intermediate to late and late dry AMD have a FDA path
- Newer outcomes are being accepted
- Other areas of the Agency have accepted “synthetic” control arm
    - Built from the control arms of historical clinical trials

FDA Draft Guidance wet AMD

Trial Design

- FDA recommends parallel-group, randomized by patient, double-masked trials in which the investigational drug group **demonstrates superiority over the control group.**

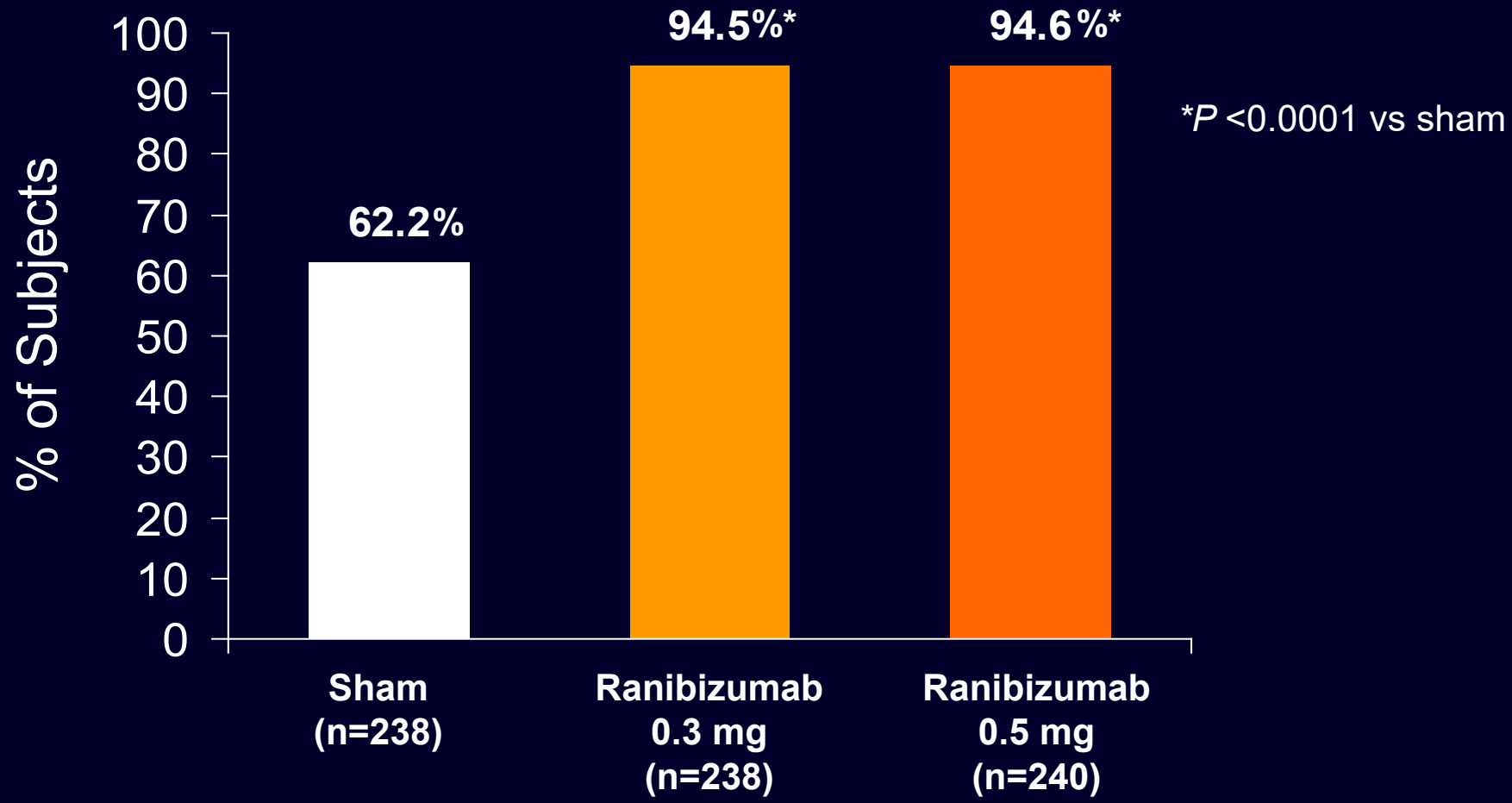
FDA Draft Guidance wet AMD

Efficacy Considerations

- A statistically significant smaller percentage of patients with a **doubling of the visual angle in best corrected distance visual acuity at 9 months or later**
- A statistically significant larger percentage of patients with a halving of the visual angle in best corrected distance visual acuity at 9 months or later
- A statistically significant difference between groups in mean best corrected distance visual acuity of 15 or more letters at 9 months or later after the start of drug administration.

Primary Endpoint:

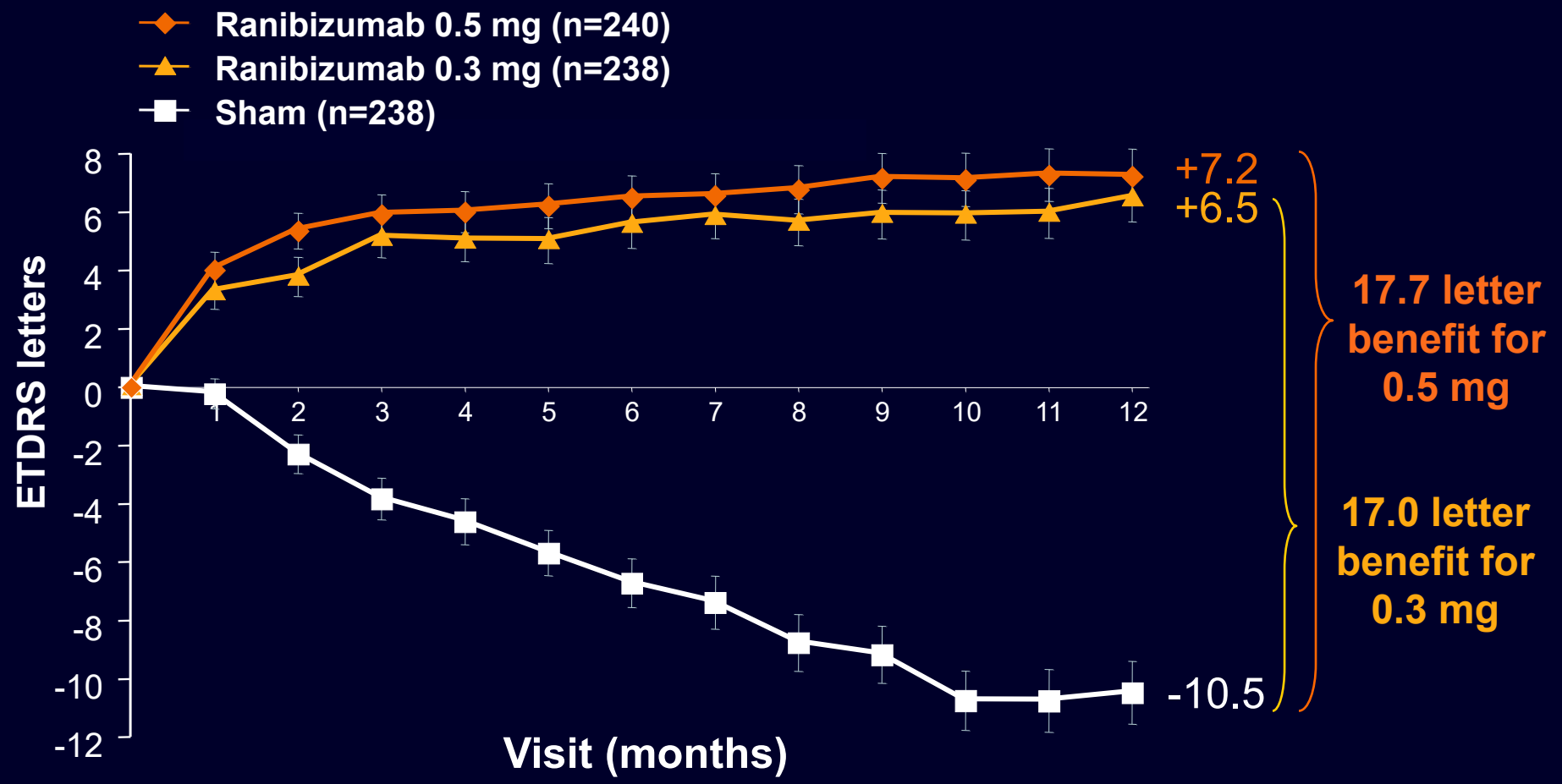
Subjects Losing <15 Letters from Baseline at Month 12



**P* <0.0001 vs sham

Secondary Endpoint:

Mean Change in Visual Acuity Over Time



P <0.0001 vs. sham at all visits for both doses

FDA Draft Guidance wet AMD

Trial Design

- FDA recommends parallel-group, randomized by patient, double-masked trials in which the investigational drug group **demonstrates superiority over the control group.**

- Alternatively, FDA recommends parallel-group, randomized by patient, double-masked trials in which the investigational drug group demonstrates **noninferiority either to ranibizumab injection administered intravitreally every 4 weeks or to aflibercept administered intravitreally either every 4 weeks or every 8 weeks** (after 3 monthly injections).

FDA Draft Guidance wet AMD

Efficacy Considerations

- A statistically significant smaller percentage of patients with a **doubling of the visual angle in best corrected distance visual acuity at 9 months or later**
- A statistically significant larger percentage of patients with a halving of the visual angle in best corrected distance visual acuity at 9 months or later
- A statistically significant difference between groups in mean best corrected distance visual acuity of 15 or more letters at 9 months or later after the start of drug administration.
- **Two-sided, 95 percent confidence** interval at 9 months or later after the start of drug administration:
  - Ranibizumab group is greater than or equal to -4.5 letters
  - Aflibercept group is greater than -4.5 letters

VIEW 1 & 2

Primary Endpoint: Prevention of Moderate Vision Loss

All doses of VEGF Trap-Eye were non-inferior to ranibizumab

*Compared to baseline; LOCF; VIEW 1 pps: Rq4 n=269; 2q4 n=285; 0.5q4 n=270; 2q8 n=265
VIEW 2 pps: Rq4 n=269; 2q4 n=274; 0.5q4 n=268; 2q8 n=270

Practical Considerations

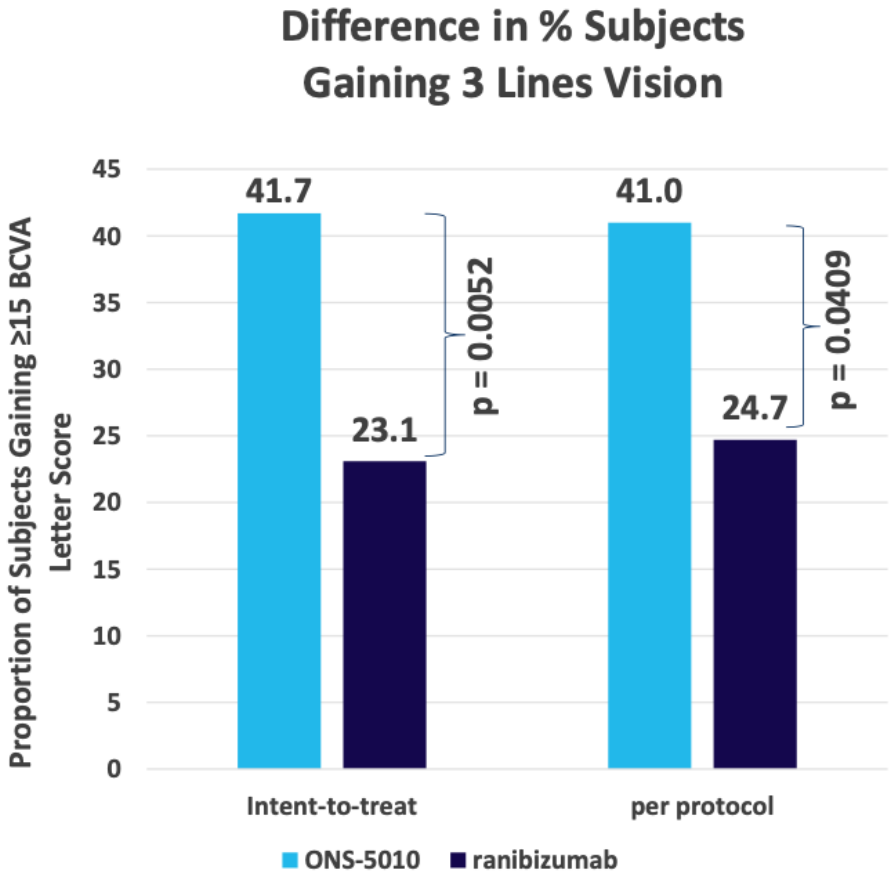
- For Non-inferiority:
    - Avastin CAN be considered an adequate control
    - Vabysmo is NOT considered an adequate control

- For Superiority:
    - All anti-VEGF can be considered as control
    - FDA requires ≥ 15 ETDRS letter improvement or prevention of worsening

Norse 2 Phase 3 Study

Primary Endpoint Met with Statistically Significant, Clinically Relevant Results[1]

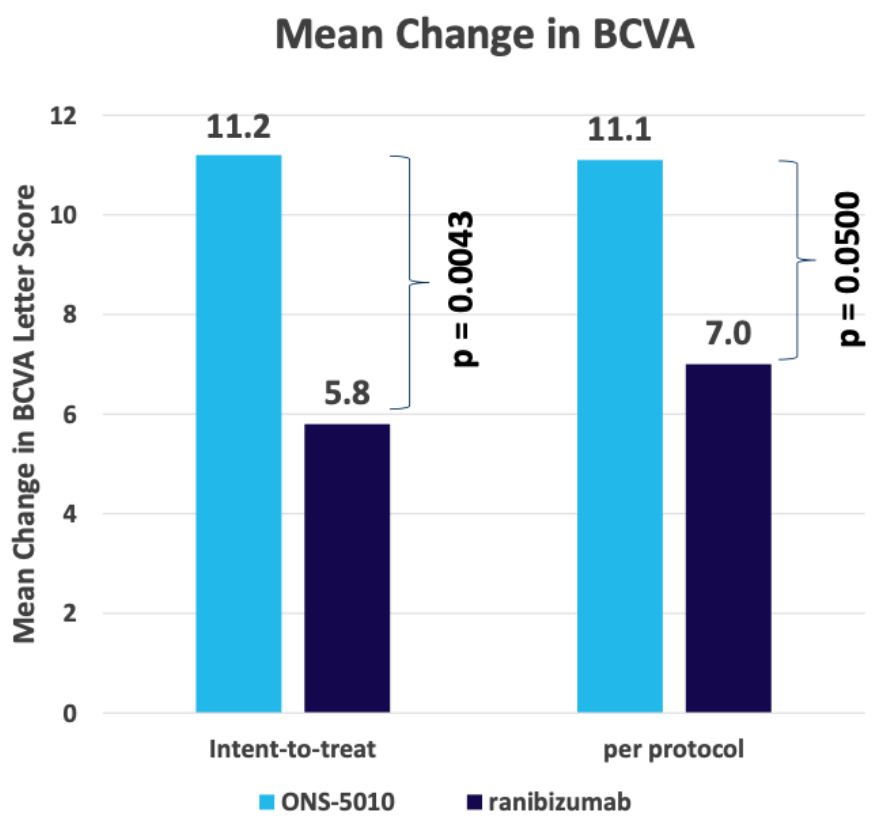
Characteristic	Statistic	ONS-5010 (n=113)	Ranibizumab (n=115)
Intent-to-Treat Pop.			
Number of Subjects	n/N (%)	**45/108 (41.7)**	24/104 (23.1)
Risk Difference		0.1859	
95% CI		(0.0442,0.3086)	
p-value		**0.0052**	
Per Protocol Pop.			
Number of Subjects	n/N (%)	34/83 (41.0)	18/73 (24.7)
Risk Difference		0.1631	
95% CI		(0.0120, 0.3083)	
p-value		**0.0409**	



Norse 2 Phase 3 Study

Key Secondary Endpoints Met with Highly Statistically Significant, Clinically Relevant Results

Characteristic	Statistic	ONS-5010 (n=113)	Ranibizumab (n=115)
BCVA Score Change from Baseline to Month 11 (ITT)	n	104	96
	Mean (SD)	**11.2 (12.19)**	5.8 (14.80)
p-value		**0.0043**	
BCVA Score Change from Baseline to Month 11 (PP)	n	80	68
	Mean (SD)	11.1 (12.77)	7.0 (14.56)
p-value		**0.0500**	



FDA Draft Guidance wet AMD

Trial Population

- For a trial designed as a **superiority trial**, the sponsor should enroll patients with neovascularization caused by age-related macular degeneration **who have had visual loss or would be expected to develop visual loss.**
- For a trial designed as a **noninferiority trial**, the sponsor should enroll patients with neovascularization caused by age-related macular **degeneration who have visual loss.**

FDA Draft Guidance wet AMD

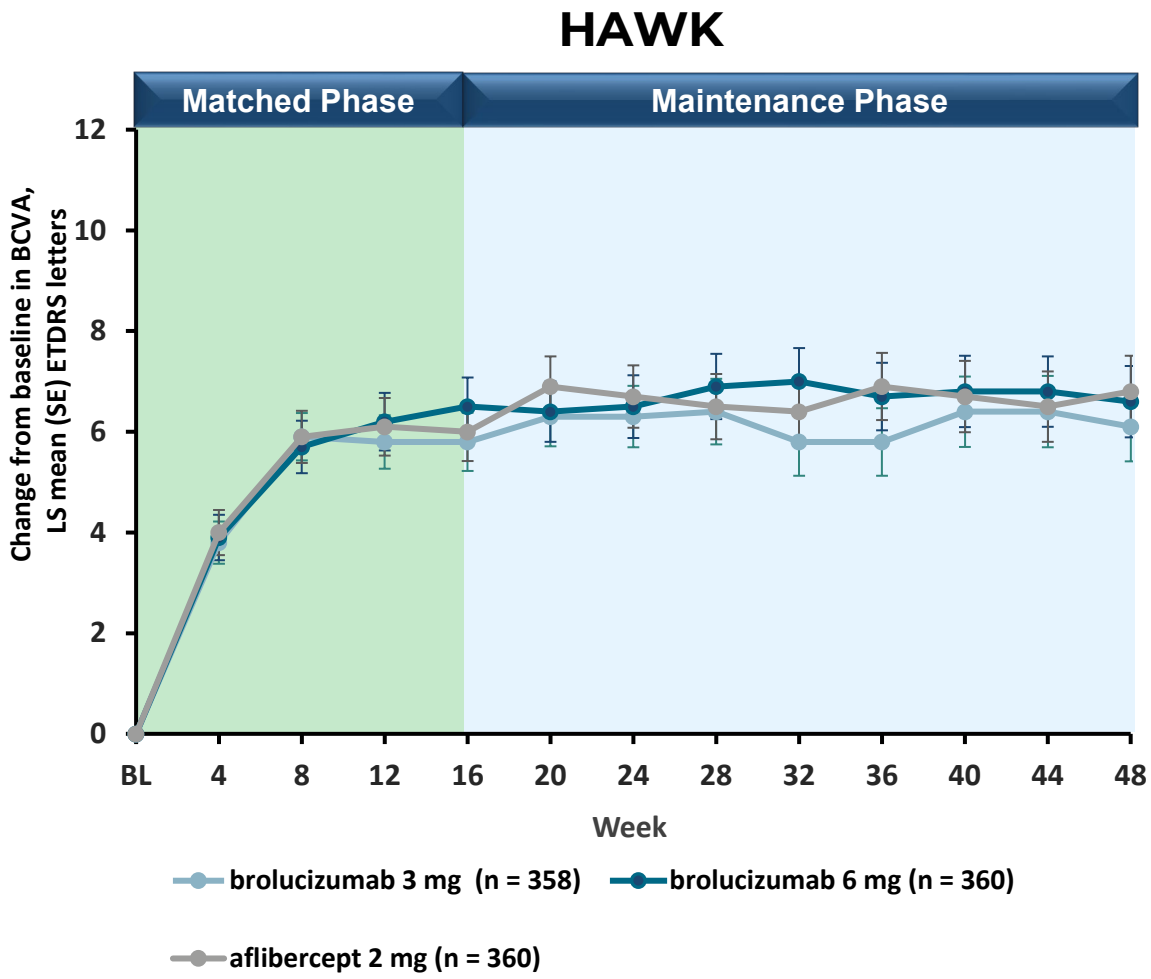
Trial Population

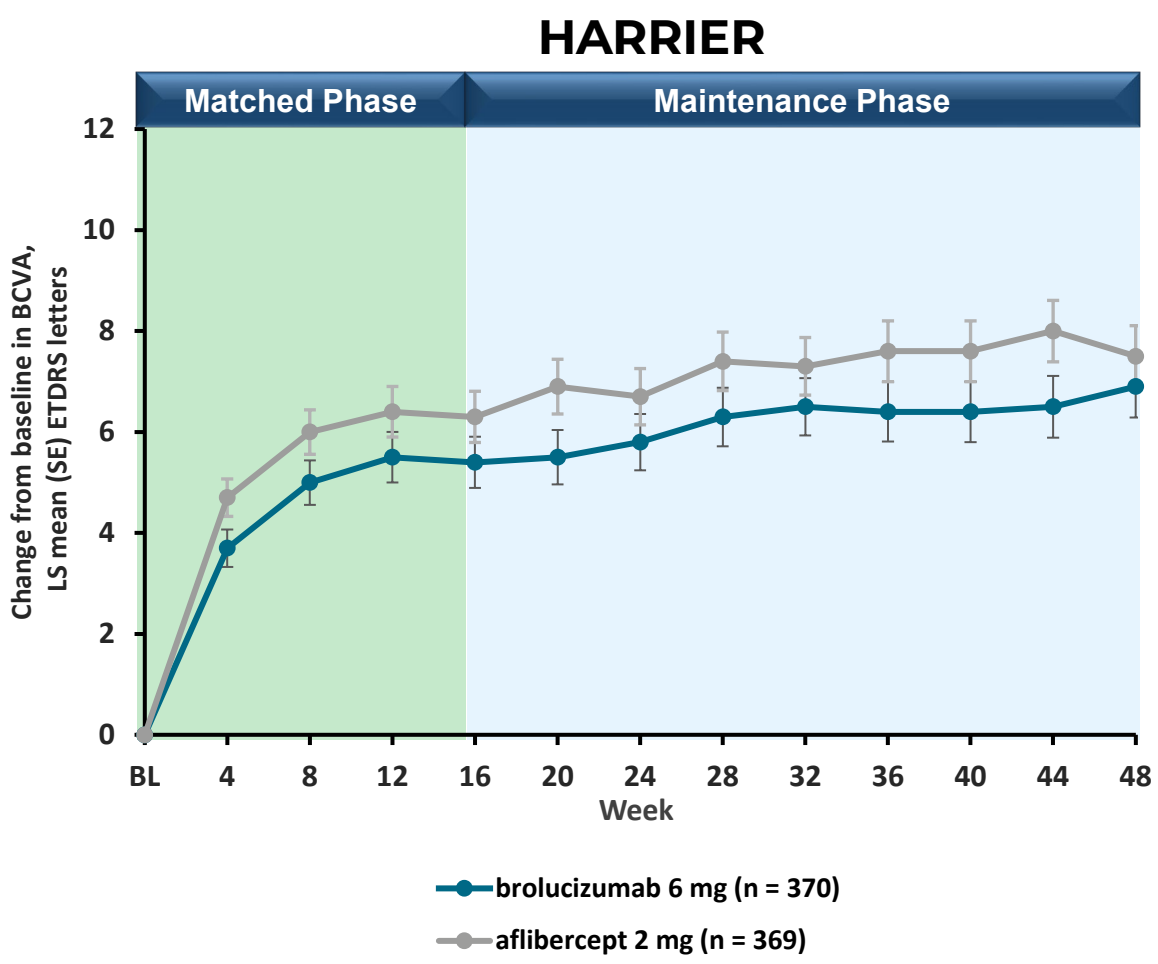
- For a trial designed as a **superiority trial**, the sponsor should enroll patients with neovascularization caused by age-related macular degeneration **who have had visual loss or would be expected to develop visual loss.**
- For a trial designed as a **noninferiority trial**, the sponsor should enroll patients with neovascularization caused by age-related macular **degeneration who have visual loss.**

Comparator

- Each investigational drug arm is expected to have **at least one other comparative arm in which the dosing frequency, criterion for dosing adjustments**, and criterion for interventions are the same.

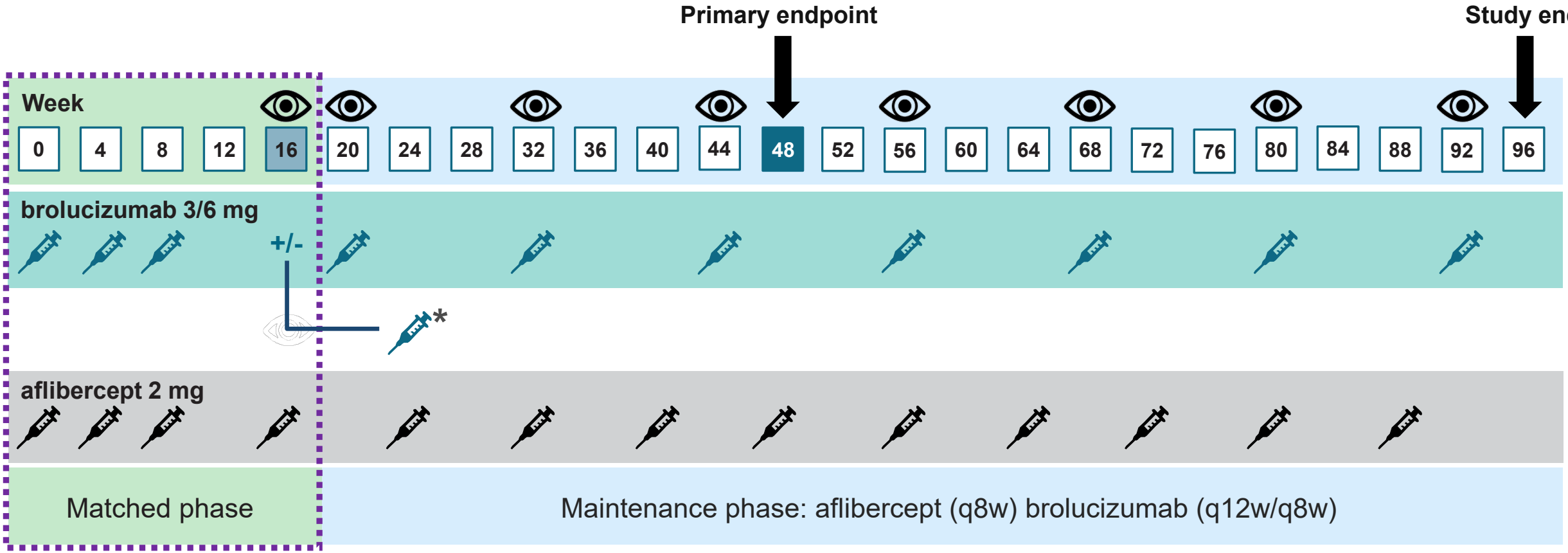
For the primary endpoint of mean change in BCVA at Week 48, brolucizumab (q12w/q8w) was non-inferior to aflibercept (q8w)





Dugel PU, et al. Ophthalmology 2020;127:72; 2. Dugel PU, et al. Ophthalmology 2020 doi: 10.1016/j.ophtha.2020.06.028. [Epub ahead of print]
Full Analysis Set, LOCF. [a]Non-inferiority (NI) margin = 4 letters. Analyzed using ANOVA model with baseline BCVA categories (≤55, 56–70, ≥71 letters), age categories (<75, ≥75 years) and treatment as fixed effect factors.
BCVA, best corrected visual acuity; BL, baseline; ETDRS, Early Treatment Diabetic Retinopathy Study. LOCF, last observation carried forward; LS, least squares; SE, standard error

HAWK and HARRIER: brolucizumab (q12w/q8w) vs aflibercept (q8w)[1,2]

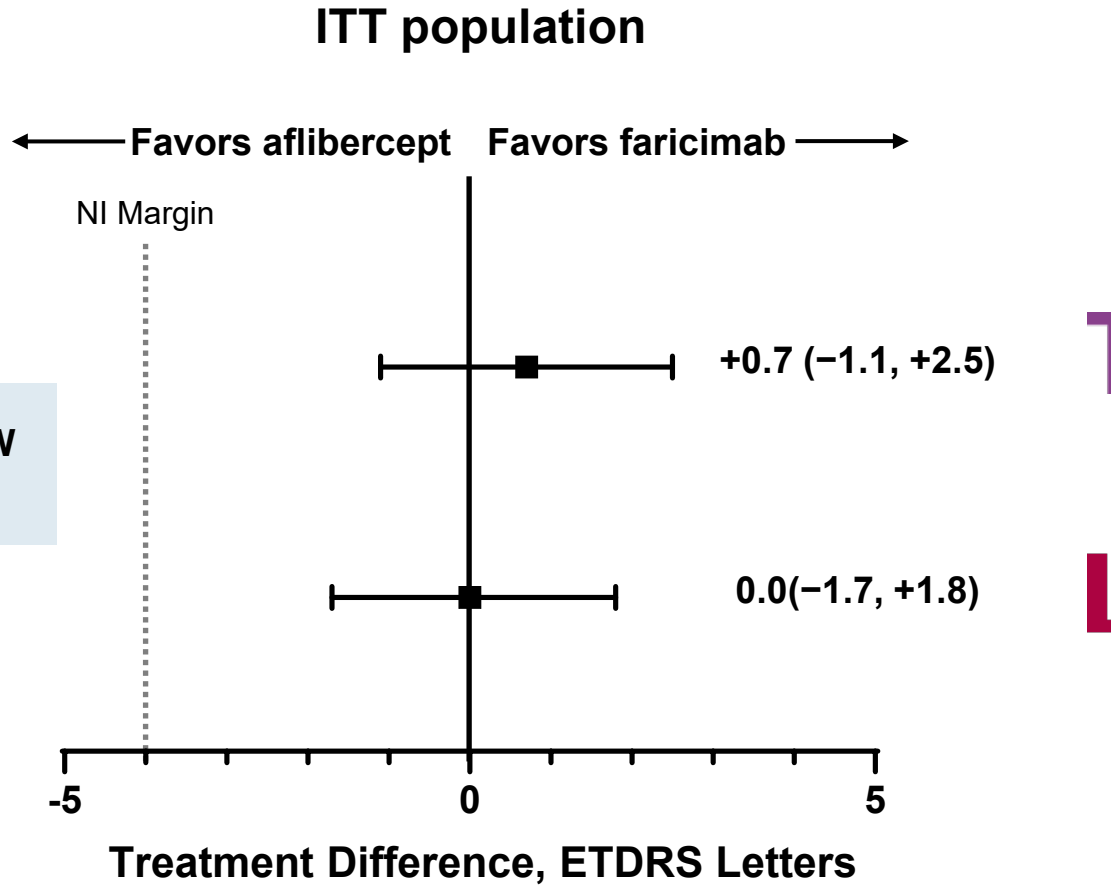


Disease activity assessment by masked investigators[a]
*If disease activity was detected at any DAA visit, patients on brolucizumab q12w were adjusted to, and remained on, a q8w regimen

1. Dugel PU, et al. Ophthalmology 2020;127:72; 2. Dugel PU, et al. Ophthalmology 2020 doi: 10.1016/j.ophtha.2020.06.028. [Epub ahead of print]
[a]Disease activity assessments were conducted at pre-specified visits by the masked investigator. Presence of disease activity was determined at the discretion of the masked investigator and supported by protocol guidance based on dynamic functional and anatomical characteristics. Additional assessments and potential dosing interval adjustments occurred at Weeks 28, 40, 52, 64, 76, and 88 in HARRIER only. Sham injections were administered to maintain masking. Visual and anatomic assessments were made prior to injections at Weeks 16 and 48. DAA, disease activity assessment; q8w, 8-week dosing interval; q12w, 12-week dosing interval

TENAYA and LUCERNE Met Primary Endpoint: BCVA Gains From Baseline With Faricimab Dosed up to Q16W Were Noninferior to Aflibercept Q8W

Faricimab up to Q16W vs aflibercept Q8W



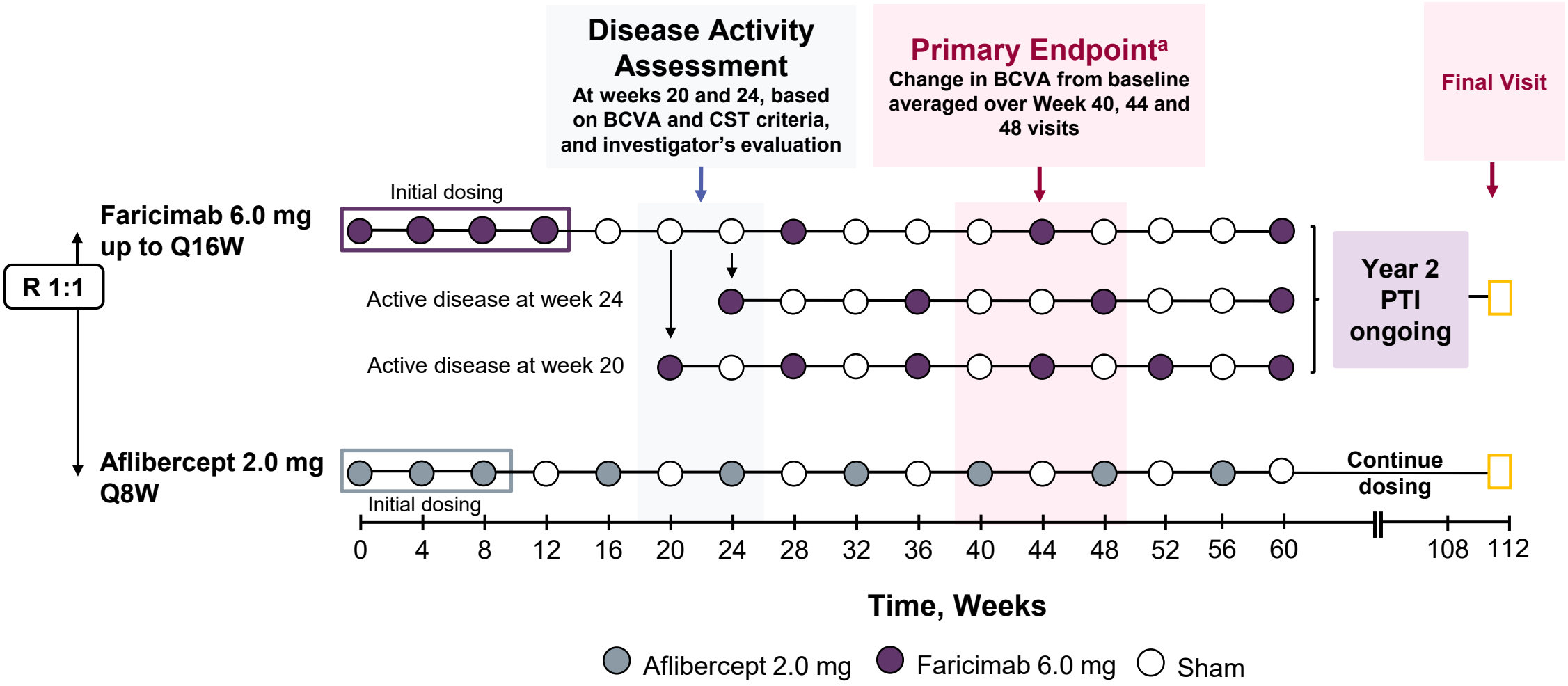
TENAYA

LUCERNE

Primary endpoint: BCVA change from baseline averaged over Weeks 40, 44, and 48

Results are based on a mixed model for repeated measures analysis. 95% CIs are shown.
BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; ITT, intent-to-treat; NI, noninferiority; Q8W, every 8 weeks; Q16W, every 16 weeks.

TENAYA and LUCERNE
Randomized, Double-Masked, Multicenter Studies Designed to Evaluate the Efficacy and Safety of Faricimab Versus Aflibercept



ClinicalTrials.gov identifiers: NCT03823287 (TENAYA); NCT03823300 (LUCERNE).

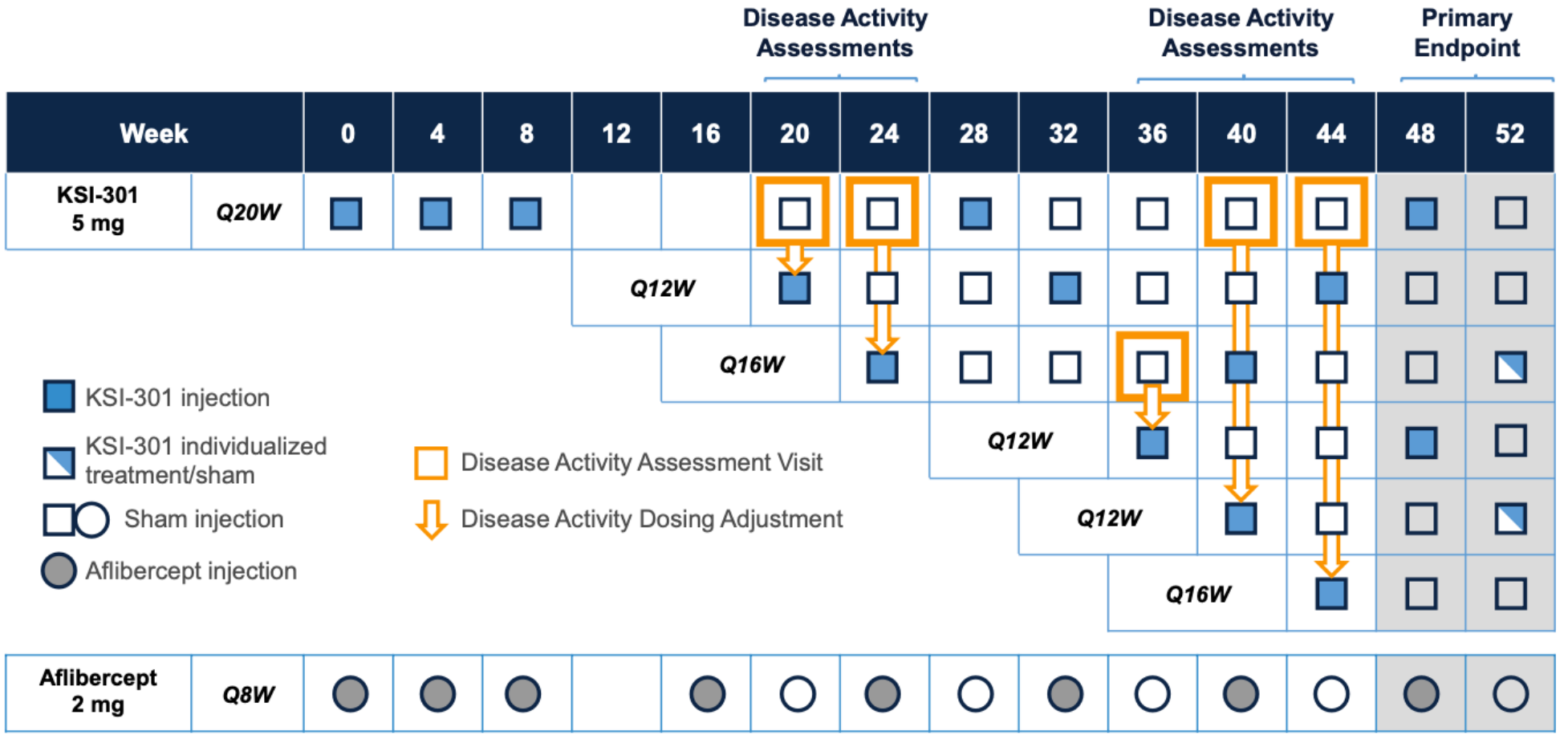
[a] BCVA was measured using the Early Treatment Diabetic Retinopathy Study visual acuity chart at a starting distance of 4 m.

BCVA, best-corrected visual acuity; CST, central subfield thickness; Q8W, every 8 weeks; Q16W, every 16 weeks; R, randomized.

TENAYA LUCERNE

KODIAK Phase 3 design

DAZZLE Study Design: Randomized, double-masked non-inferiority study of KSI-301 every 3 to 5 months vs aflibercept every 2 months in treatment-naïve wet AMD patients



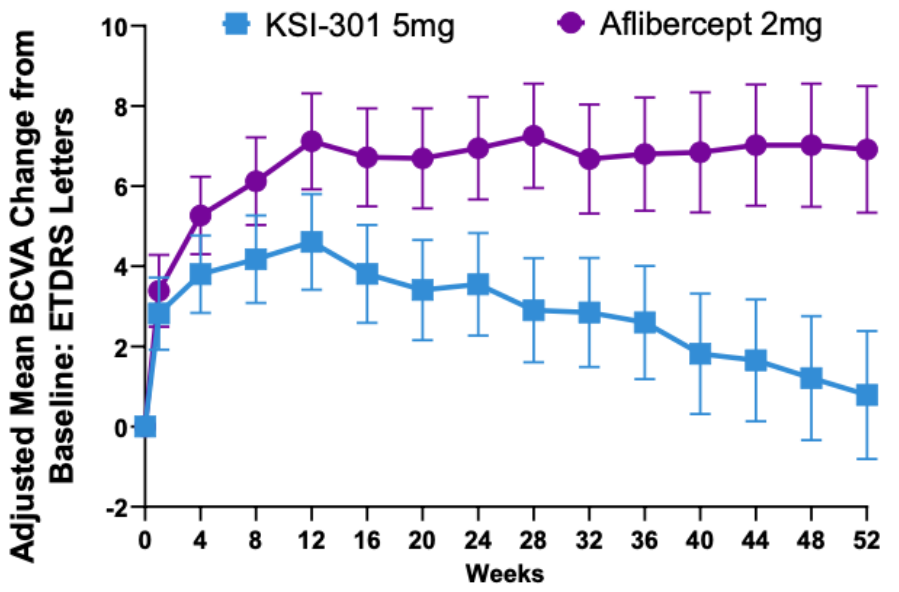
Clinicaltrials.gov, study identifier: NCT04049266
AMD: age-related macular degeneration; Q8W: every 8 weeks, Q12W: every 12 weeks; Q16W; every 16 weeks; Q20W: every 20 weeks.

KODIAK Phase 3 design

BCVA and OCT Outcomes

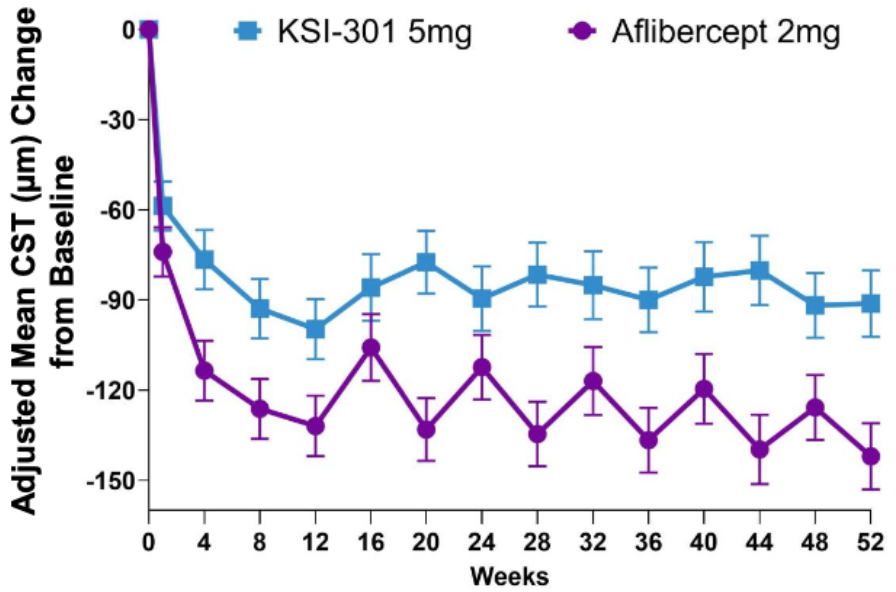
The study did not meet its primary endpoint of non-inferiority in BCVA

BCVA Change Over Time



	Average of weeks 48 & 52
KSI-301 5mg	1.0 (-0.5, 2.5)*
Aflibercept 2mg	7.0 (5.5, 8.5)*

OCT / CST Change Over Time



	Average of weeks 48 & 52
KSI-301 5mg	-91.5 (-102, -81)*
Aflibercept 2mg	-133.9 (-144.5, -123.4)*

Least square means BCVA change from baseline and 95% CI are based on MMRM model with treatment, visit, baseline BCVA categories, BCVA-low luminance VA baseline categories, geographical location categories, and treatment by visit interaction. Least square means CST change from baseline and 95% CI are based on MMRM model with treatment, visit, baseline OCT, baseline BCVA categories, BCVA-low luminance VA baseline categories, geographical location categories, and treatment by visit interaction. *Adjusted mean BCVA/CST change from baseline at year 1, averaged over weeks 48 and 52.
BCVA: best corrected visual acuity; ETDRS: early treatment diabetic retinopathy study; OCT: optical coherence tomography; CST: central subfield thickness.

Practical Considerations

- HAWK/HARRIER and TENAYA/LUCERNE would not be allowed anymore
- For every “different” dosing arm in the study arm, a similar control arm with same dosing must be enrolled.
    - This could mean dosing the control arm at an “off-label” dosing regimen or duration
- Moreover, the Agency does not consider a sham injection as adequate for masking a patient

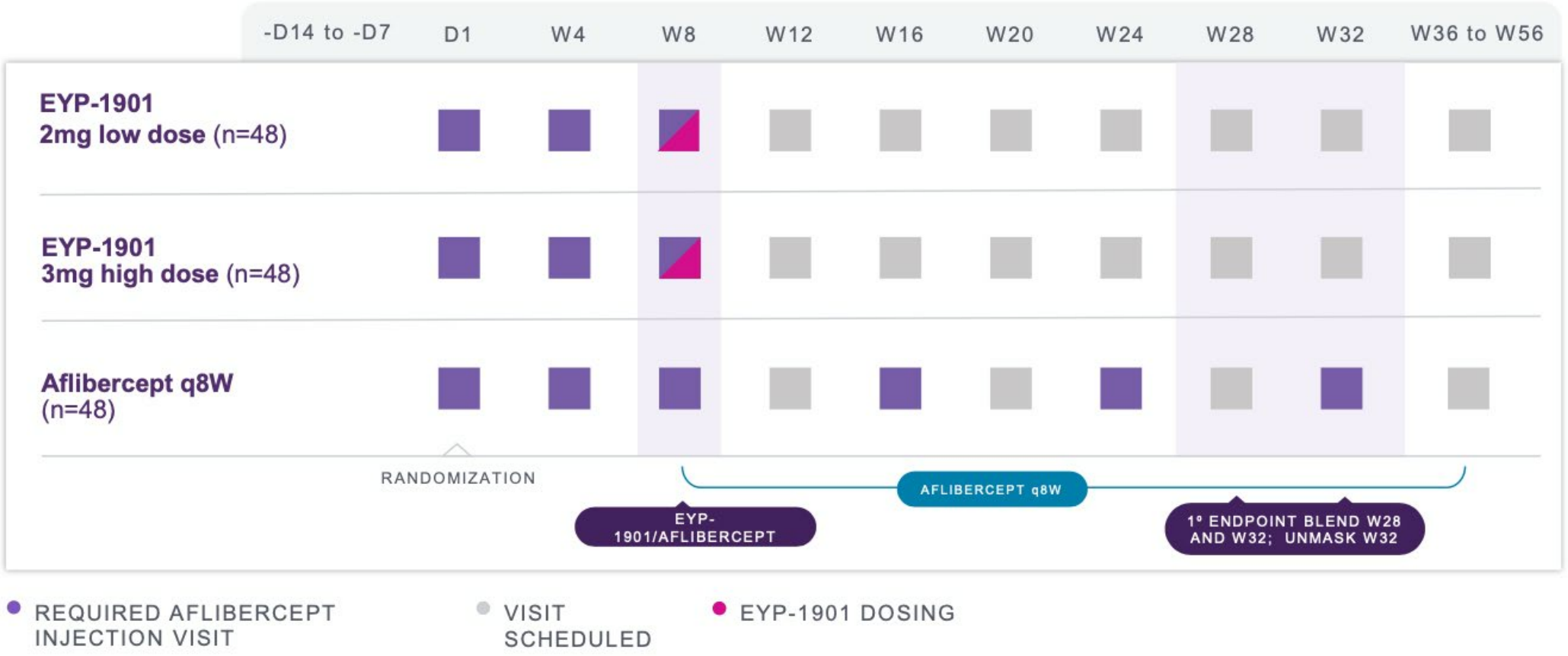
FDA Draft guidance Highlights

Efficacy Considerations

- A statistically significant smaller percentage of patients with a **doubling of the visual angle in best corrected distance visual acuity at 9 months or later**
- A statistically significant larger percentage of patients with a halving of the visual angle in best corrected distance visual acuity at 9 months or later
- A statistically significant difference between groups in mean best corrected distance visual acuity of 15 or more letters at 9 months or later after the start of drug administration.
- **Two-sided, 95 percent confidence** interval at 9 months or later after the start of drug administration:
  - Ranibizumab group is greater than or equal to -4.5 letters
  - Aflibercept group is greater than -4.5 letters
- A **decrease in the number of administrations** of available effective therapies alone **is not sufficient** for the demonstration of efficacy.

Sustained Release Conundrum

EYP-1901 DAVIO 2 clinical trial is non-pivotal randomized, double-masked, aflibercept controlled



Conclusions

- Dry AMD guidance has not been published
- Wet AMD Draft guidance changes how future clinical trials need to be performed
- As additional validation studies are performed these guidelines will change

Thank you