The Results of the CATALINA Phase 2 Study of NGM621 for Geographic Atrophy Secondary to AMD

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Retina Society 2022 Annual Meeting, Pasadena, CA

Financial Disclosures

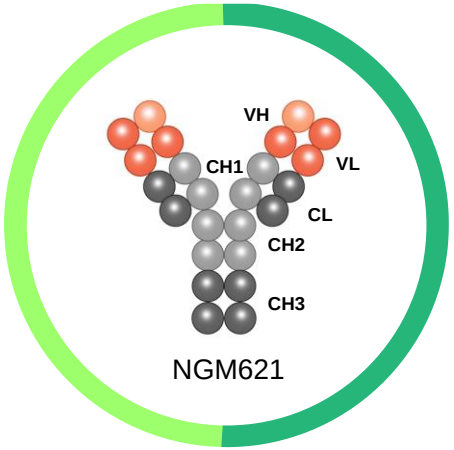
- CCW: 4DMT (C, R), Abbvie (C), Adverum (C,R), Aerie (C,R), AffaMed (R), AGTC (C), Alcon (C), Alexion (R), Alimera (C,R), Allergan (C,R), Allgenesis (C, R), Annexon (C,R), Apellis (C, R), Asclepix (R), Bausch + Lomb (C), Bayer (C,R), Bionic Vision (C), Boehringer Ingelheim (C,R), Kanghong (C,R), Cholgene (C), Clearside (C,R), Curacle (C), EyePoint (C, R), Foresite (C), Frontera (C), Gemini (R), Genentech (C,R), Gyroscope (C,R), IACTA (C), IONIS (R), IVERIC (C,R), Janssen (C), Kato (C), Kiora (C), Kodiak (C,R), Kriya (C), LMRI (R), Merck (C), Nanoscope (C,R), Neurotech (R), NGM (C,R), Novartis (C, R), OccuRx (C), OcuTerra (C, R), Ocular Therapeutix (C, R), Ocuphire (R), ONL (C, SO), Opthea (C,R), Oxurion (R), Palatin (C), PerceiveBio (C), Perfuse (C), PolyPhotonix (C, SO), Ray (C), RecensMedical (C, R, SO), Regeneron (C,R), RegenXBio (C,R), Resonance (C), Roche (C, R), Stealth (C), Surrozen (C), THEA (C), TissueGen (SO), UNITY (R), Valo (C), Visgenx (SO), Vitranu (SO)
- C=Consultant, R= Research Grants, SO = Stock Options

Study Disclosures:

This study includes research conducted on human subjects

- Institutional Review Board approval was obtained prior to study initiation
- Funding was provided by NGM Biopharmaceuticals

NGM621: Anti-Complement C3 Antibody



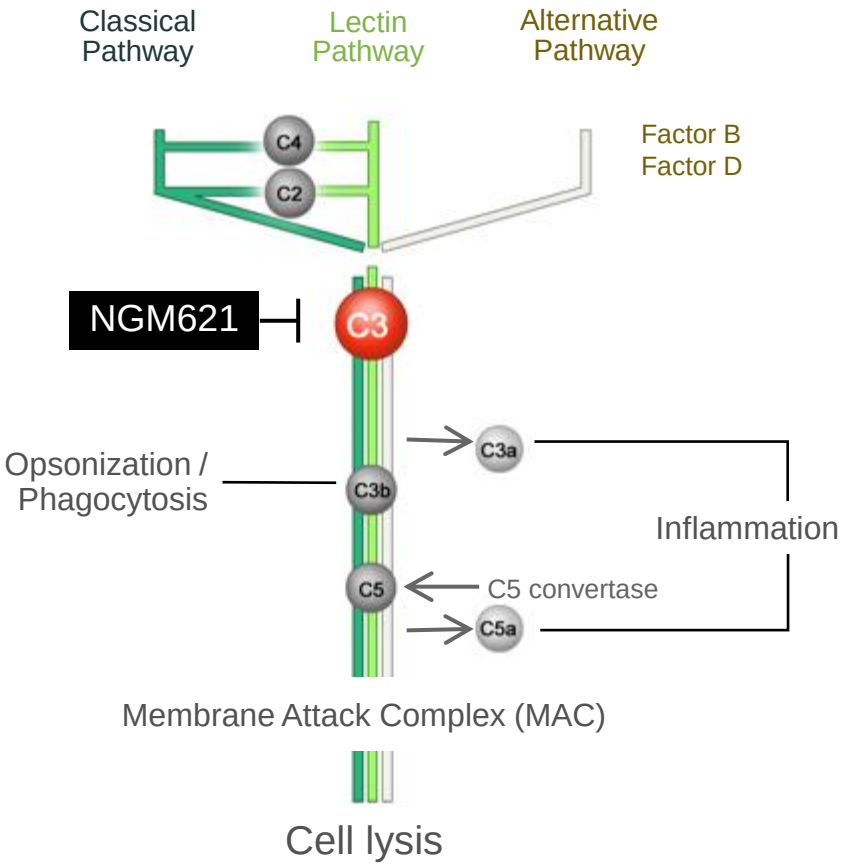
NGM621 MOLECULE ATTRIBUTES

Type	Humanized IgG1 monoclonal antibody
Target	Complement C3 and C3b
MW	~150 kDa
Affinity	K_D = 340pM
Effector Function	Fc mutations eliminating effector function

SCIENTIFIC RATIONALE: **NGM621 FOR GEOGRAPHIC ATROPHY**

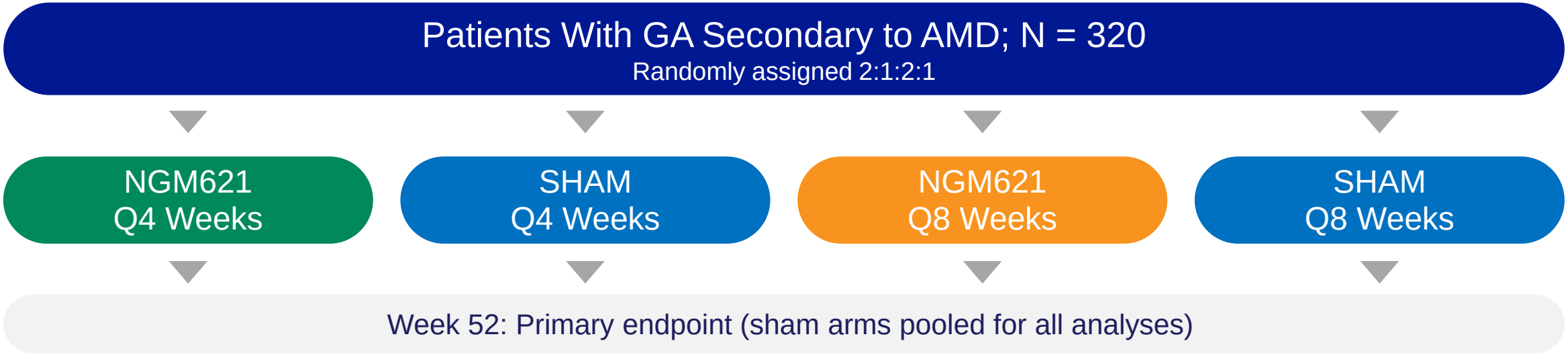
- Dysregulated activation of the complement system has been implicated in the onset and progression of GA
- C3 is a central component of the complement system, and the first point of convergence for all three initiating pathways
- NGM621 is a novel monoclonal antibody that potently inhibits C3, effectively blocking all downstream complement signaling

COMPLEMENT CASCADE



IgG1 = immune globulin G1

Phase 2 CATALINA Study Design



PRIMARY ENDPOINT	The rate of change in GA lesion area (slope) as measured by fundus autofluorescence over 52 weeks of treatment
DESIGN	Multicenter, randomized, double-masked, sham-controlled, overseen by an independent data safety monitoring board

IVT = intravitreal; Q4 = every 4 weeks; Q8 = every 8 weeks

CATALINA Key Inclusion and Exclusion Criteria

KEY INCLUSION CRITERIA

- ≥ 55 years of age
- BCVA ≥ 34 ETDRS letters (20/200 or better Snellen equivalent)
- Clinical diagnosis of GA secondary to AMD
  - Foveal and non-foveal lesions allowed
- Study Eye GA requirements:
  - Well demarcated GA, imaged in its entirety
  - Total GA area between ≥2.5 mm^2 and ≤17.5 mm^2
  - If multifocal, at least one lesion must be ≥1.25mm^2
  - Presence of banded or diffuse junctional hyperautofluorescence
  - No evidence of current or prior CNV

KEY EXCLUSION CRITERIA

- GA secondary to a condition other than AMD in either eye
- Any history or active ocular infection in either eye within 3 months of randomization
- PDR or DME in either eye

Fellow (non-study) eye CNV permitted if clinical diagnosis was ≥ 2 years prior; capped at not more than 25% of study population

BCVA = best corrected visual acuity; DME = diabetic macular edema; ETDRS = early treatment diabetic retinopathy study; PDR = proliferative diabetic retinopathy

Patient Disposition

	NGM621 Q4W (N = 108)	NGM621 Q8W (N = 105)	Sham Pooled (N = 107)	Total (N = 320)
PATIENT DISPOSITION				
Subjects randomized, n (%)	108	105	107	320
Subjects treated, n (%)	108 (100%)	104 (99.0%)	106 (99.1%)	318 (99.4%)
DISCONTINUATIONS				
Completed study treatment through 52 weeks, n (%)	93 (86.1%)	89 (84.8%)	93 (86.9%)	275 (85.9%)
Discontinued study treatment prior to 52 weeks, n (%)	15 (13.9%)	16 (15.2%)	14 (13.1%)	45 (14.1%)
EXPOSURE				
Total Number of injections Received per Subject, Mean(SD)	11.5 (2.76)	6.3 (1.59)	9.1 (3.24)	9.0 (3.38)
% of Scheduled Treatment[1]	99.1	98.8	99.4	99.1

Overall high treatment compliance rate of 98-99%

[1]Percentage calculated as: The (total number of injections received divided by the total number of scheduled injections)*100

Patient Demographics and Baseline Ocular Characteristics

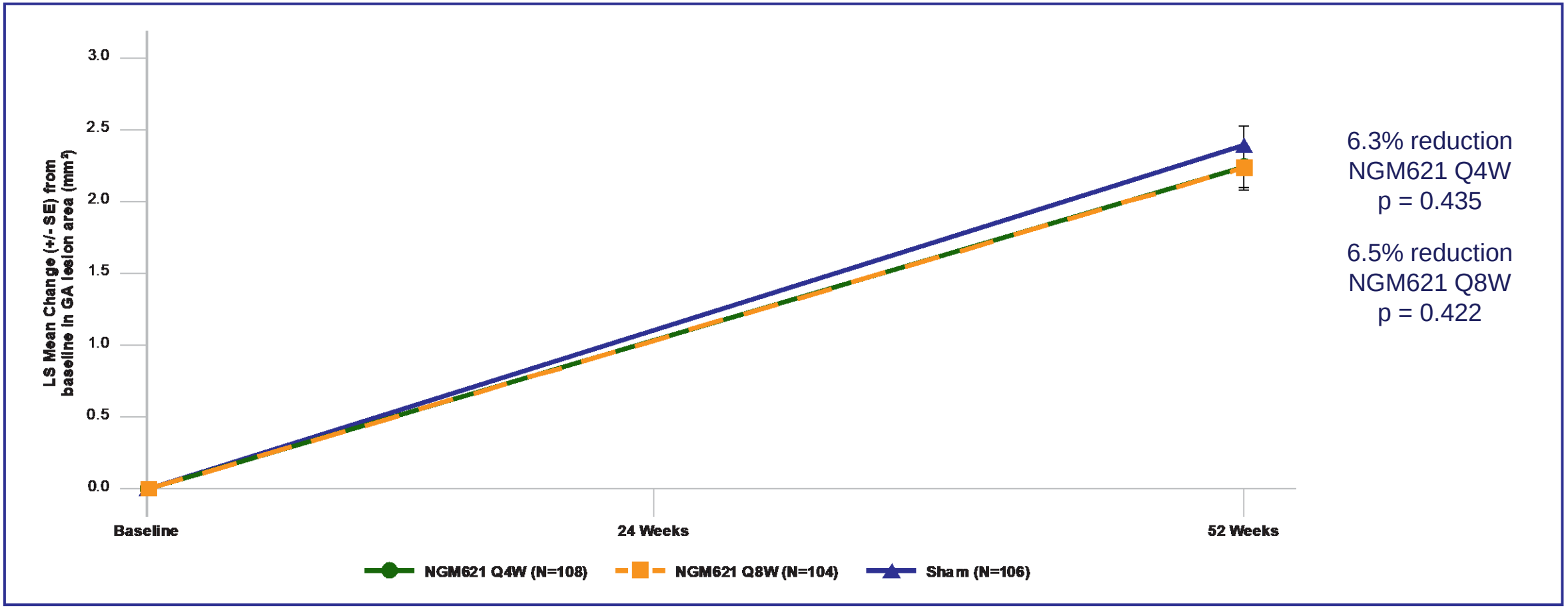
	NGM621 Q4W (N = 108)	NGM621 Q8W (N = 104)	Sham Pooled (N = 106)	Total (N = 318[2])
Age, mean (SD)	78.5 (8.17)	79.1 (7.51)	77.6 (8.42)	78.4 (8.04)
Female, n (%)	67 (62.0)	63 (60.6)	68 (64.2)	198 (62.3)
White, n (%)	107 (99.1)	102 (98.1)	101 (95.3)	310 (97.5)
GA area, mean (SD) mm^2	7.02 (3.964)	7.62 (3.968)	7.75 (4.007)	7.46 (3.980)
GA area, median mm^2	6.08	6.87	6.91	6.48
Square Root GA area, mean (SD) mm^2	2.56 (0.699)	2.67 (0.708)	2.69 (0.710)	2.64 (0.706)
Foveal Involved GA (%)	62 (57.4%)	65 (62.5%)	66 (62.3%)	193 (60.7%)
Multifocal lesions (%)	58 (53.7%)	56 (53.8%)	51 (48.1%)	165 (51.9%)
BCVA, mean (SD) ETDRS letters	62.8 (14.73)	58.4 (15.33)	60.6 (14.20)	60.6 (14.82)
Snellen Equivalent	20/63	20/80	20/63	20/63
LLD (BCVA - LLVA), mean ETDRS letters	29.9 (16.82)	29.4 (16.60)	27.1 (16.10)	28.8 (16.50)
Bilateral GA, n (%)	99 (91.7)	88 (84.6)	95 (89.6)	282 (88.7)
CNV in Fellow Eye, n (%)[1]	22 (20.4)	17 (16.3)	20 (18.9)	59 (18.6)

[1]Fellow Eye CNV is defined as a history of CNV or neovascular AMD
[2]The mITT analysis set includes all randomized and treated (with at least one study treatment) patients
LLD = low luminance deficit; LLVA = low luminance visual acuity

Results and Interpretation

Primary Endpoint Analysis – Slope Analysis

Rate of Change in GA Lesion Area over 52 Weeks



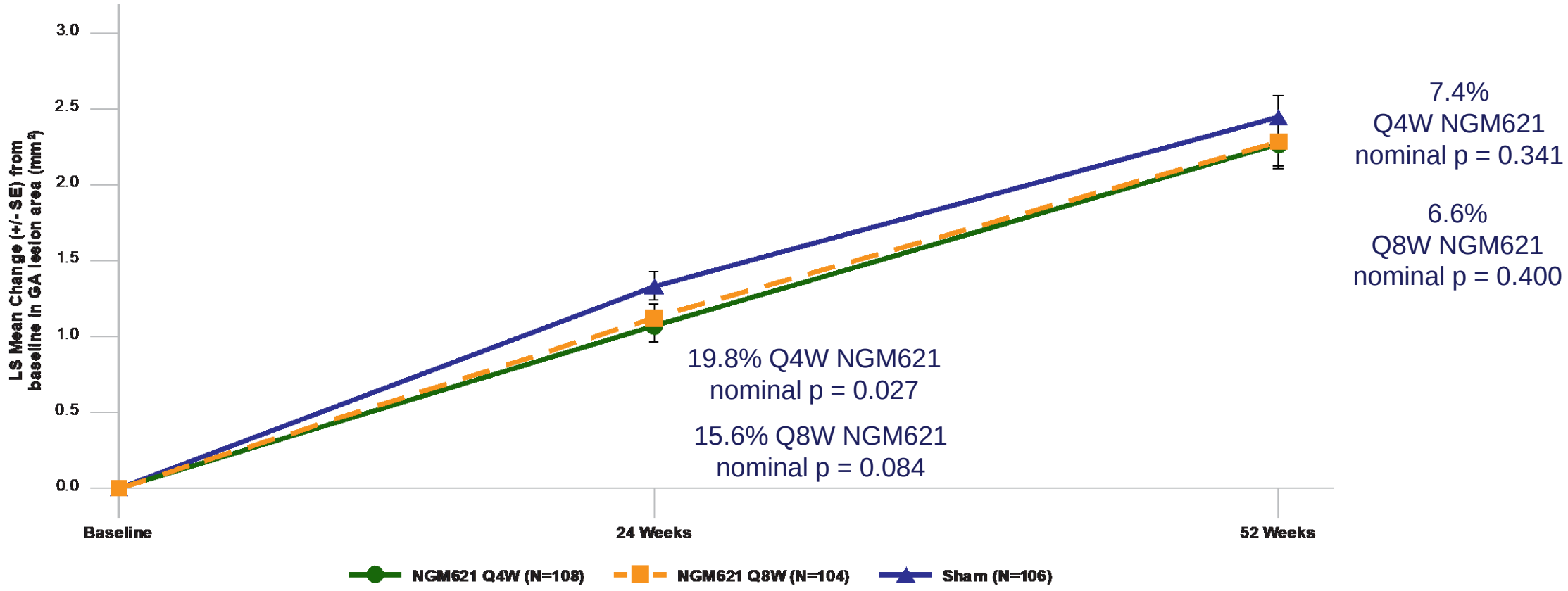
6.3% reduction
NGM621 Q4W
p = 0.435

6.5% reduction
NGM621 Q8W
p = 0.422

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

Pre-specified Secondary Analysis – MMRM Analysis

Change from Baseline in GA Lesion Area 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

Observations & Rationale for Post-Hoc Analyses

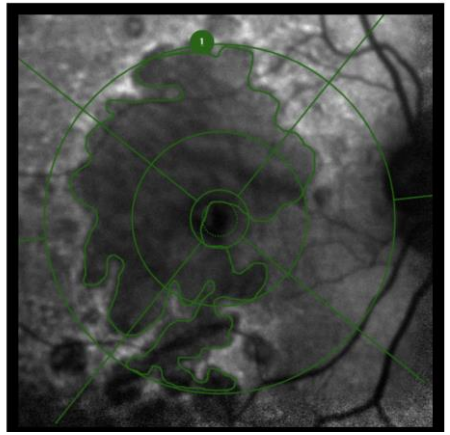
- **INITIAL HYPOTHESES TO INTERPRET THE RESULTS (not necessarily mutually exclusive):**
  - The NGM621 treatment effect may be very modest
  - The results may have been impacted by high patient variability & grading methodologies

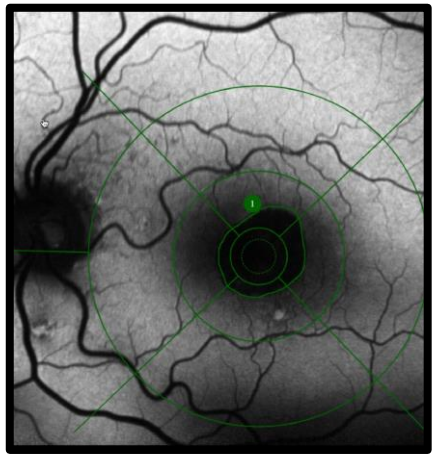
- **OBSERVATIONS:**
  1. Sham GA lesion growth trajectory slowed down in the second 6 months
  2. Some individual patient GA growth curves looked atypical; plateau or negative growth trajectories
  3. GA lesion growth appeared to be most impacted by specific GA lesions types:
     - Large and complex
     - Small and central

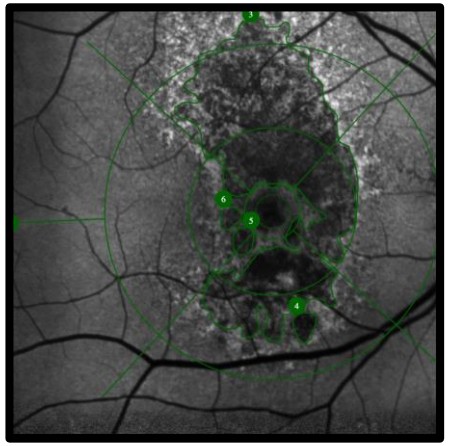
- **ACTION PLAN:**
  - Better understand the patients enrolled and the reading center methodologies

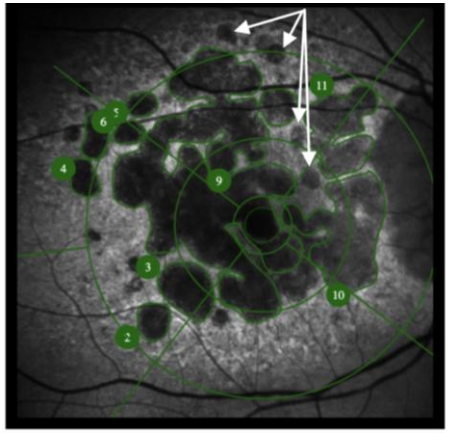
Understanding the FAF Grading Challenges & Methodology

1. Some lesions were included that did not meet eligibility criteria
   - Lesion too large or not fully captured on imaging
   - Did not demonstrate junctional diffuse or banded hyper-AF
2. Grading methodology
   - An ETDRS grid was placed on the FAF to define the grading field
   - GA was measured only within the grid
   - Led to GA areas being excluded from both contiguous & non-contiguous lesions
3. Satellite GA lesions were only included if they exceeded 430uM in diameter
4. Boarders of GA can be challenging to identify, especially when image quality is not ideal









Summary of Challenge & Paths Forward

- **BASED ON THESE LEARNINGS**
  - Data interpretation may be challenged by GA lesions enrolled and grading methodology

- **POTENTIAL PATHS FORWARD**
  1. This is very fresh data; active interpretations and additional analyses are ongoing
  2. Plans for working with the Reading Center to further evaluate GA lesions enrolled as well as grading methodology. Next steps TBD.
  3. Perform post–hoc analyses with the current data to try to better understand the efficacy of NGM621 within a patient population with more consistent FAF grading

Post hoc Analyses

Accounting for Potential Eligibility Deviations

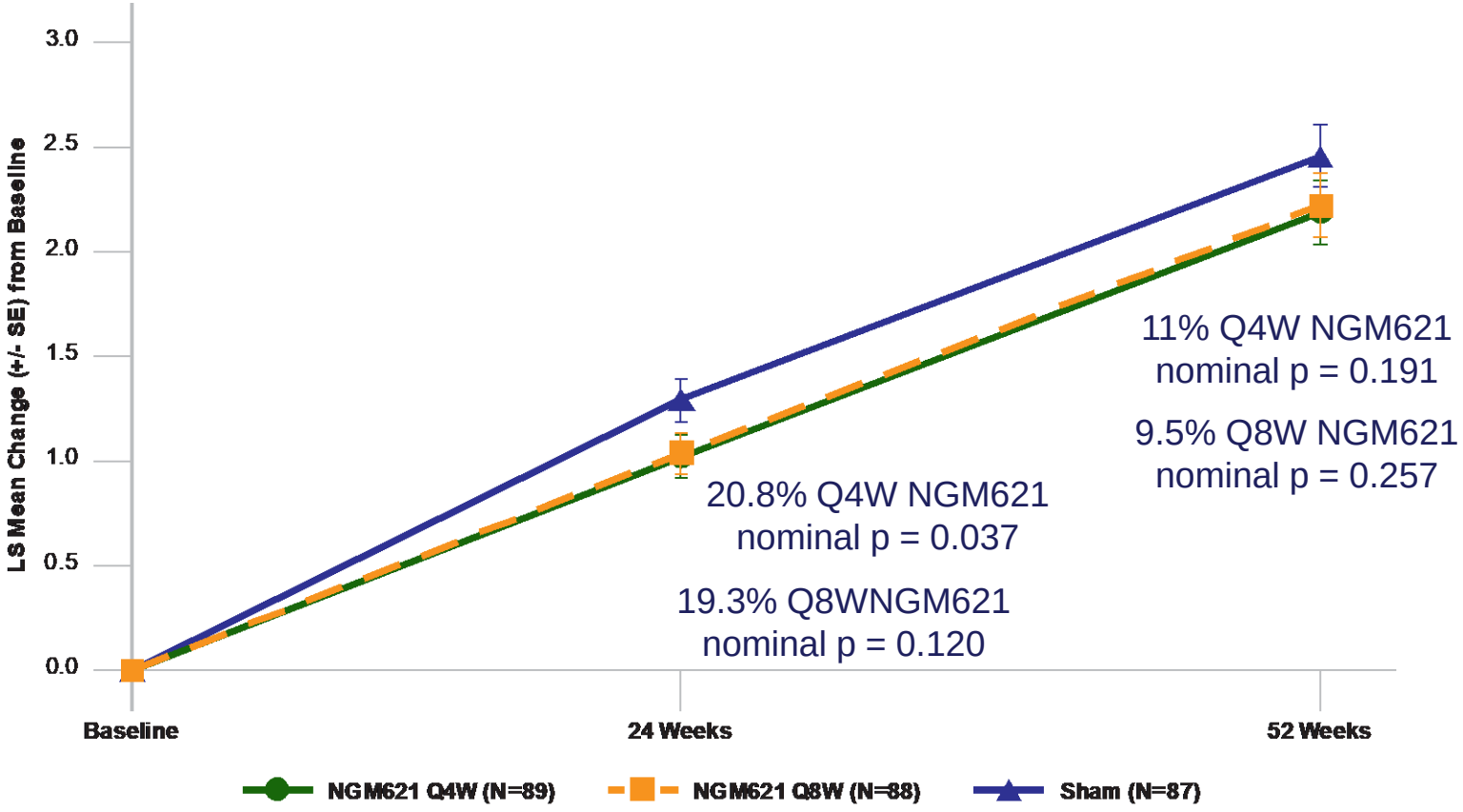
Post-hoc Masked Independent FAF Review: Excluding Patients Not Meeting 4 Specific Inclusion Criteria

- Based upon a preliminary review by an independent, masked imaging expert, 54 (17%) patients appear to not meet eligibility criteria

- Entry criteria violations:
  - Entire GA not fully contained in image window (N = 19)
  - Junctional hyper-autofluorescence not diffuse or banded pattern (N = 29)
  - GA not well demarcated (N = 1)
  - GA too large (N = 5)

- These errors appear to be distributed similarly across all arms

Patients Meeting Eligibility Subgroup Analysis
Change from Baseline in GA Area, MMRM Analysis (N = 264)

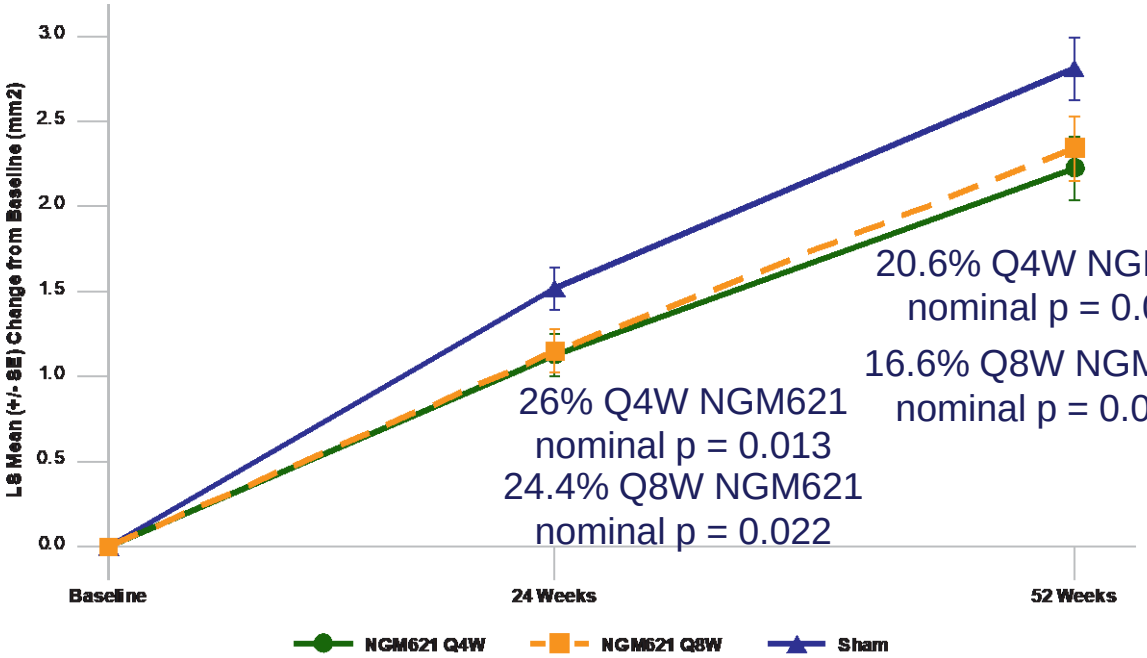


Accounting for FAF Grading Limitations

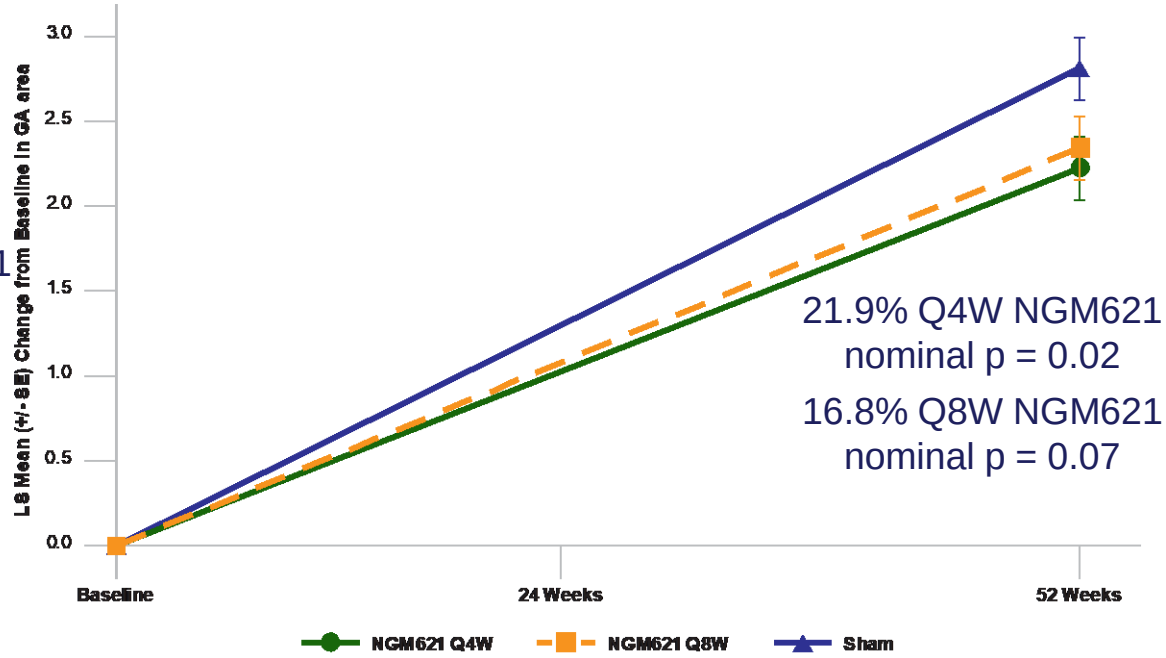
Post-hoc Quartile Analysis by Baseline GA Lesion Area: Middle 2 Quartiles (4.17 – 9.64mm^2)

Sub-population of patients least likely to be impacted by FAF grading limitations

Change from Baseline in GA Area, MMRM Analysis (N = 160)



Rate of Change in GA Area, Slope Analysis (N = 160)



ADJUSTED TREATMENT ARM (N=160)	BASELINE GA LESION AREA, MEAN (SD)
Q4W (N = 55)	6.71 mm^2 (1.63)
Q8W (N = 52)	6.62 mm^2 (1.68)
Sham (N = 53)	6.68 mm^2 (1.46)

Safety Analyses

Overall Safety: Treatment Emergent Adverse Events (TEAEs)

	NGM621 Q4W (N = 108)	NGM621 Q8W (N = 104)	Sham Pooled (N = 106)
Any TEAEs, n (%)	90 (83.3%)	88 (84.6%)	83 (78.3%)
Any Treatment-related TEAE	7 (6.5%)	5 (4.8%)	1 (0.9%)
Any SAEs, n (%)	32 (29.6%)	24 (23.1%)	29 (27.4%)
Study eye, n (%)	8 (7.4%)	8 (7.7%)	3 (2.8%)
Fellow eye, n (%)	2 (1.9%)	1 (1.0%)	2 (1.9%)
Non-ocular, n (%)	23 (21.3%)	18 (17.3%)	24 (22.6%)
Drug-related SAEs, n (%)	0	0	0
Any Ocular TEAEs			
Study eye, n (%)	57 (52.8%)	51 (49.0%)	49 (46.2%)
Fellow eye, n (%)	37 (34.3%)	28 (26.9%)	32 (30.2%)
Non-ocular TEAEs			
Patients, n (%)	67 (62%)	76 (73.1%)	67 (63.2%)
Any TEAE leading to study discontinuation, n (%)	8 (7.4%)	5 (4.8%)	6 (5.7%)
Any TEAE leading to death, n (%)	4 (3.7%)	2 (1.9%)	2 (1.9%)

Ocular SAEs in the Study Eye

	NGM621 Q4W (N = 108)	NGM621 Q8W (N = 104)	Sham Pooled (N = 106)
NUMBER OF SUBJECTS WITH ≥1 OCULAR SAE[1,2]	**8 (7.4%)**	**8 (7.7%)**	**3 (2.8%)**
Visual Acuity Reduced	2 (1.9%)	3 (2.9%)	0
Dry AMD	4 (3.7%)	3 (2.9%)	2 (1.9%)
Visual Impairment	1 (0.9%)	2 (1.9%)	1 (0.9%)
Neovascular AMD	1 (0.9%)	0	0
Retinal Artery Occlusion	1 (0.9%)	1 (1.0%)	0

86% (18/21) were protocol-defined SAEs due to loss of > 30 ETDRS letters, all due to GA progression

No SAEs were deemed related to NGM621 by the Investigator

[1]Protocol defined sight threatening events (a decrease of visual acuity of >30 letters in any post-baseline visit; severe intraocular inflammation; adverse events that require surgical or medical intervention to prevent permanent loss of sight; any decrease to light perception or worse lasting more than an hour) were reported as serious adverse events
[2]Some subjects had more than one event

Intraocular Inflammation (IOI) in the Study Eye

	NGM621 Q4W (N = 108)	NGM621 Q8W (N = 104)	Sham Pooled (N = 106)
Number of subjects with IOI[1]	1 (0.9%)	1 (1.0%)	1 (0.9%)
Number of events with IOI:	2 (1.9%)	1 (1.0%)	1 (0.9%)
Anterior Chamber Cells	1 (0.9%)[2]	1 (1.0%)	1 (0.9%)
Vitreous Cells	0	0	0
Eye Inflammation	1 (0.9%)[2]	0	0
Endophthalmitis	0	0	0
Retinal Vasculitis	0	0	0
Retinal Vein Occlusion	0	0	0

- **Anterior Chamber Cells:** All cases mild: 1 trace; 1 rare; 1 mild. Two treated with short course topical corticosteroid drops. All continued IP treatment with resolution.
- **Eye Inflammation:** Mild, bilateral. Resolved with short course topical corticosteroid drops OU. IP re-started without recurrence of IOI.

[1]Intraocular inflammation (IOI) defined as inflammation, anterior chamber cells, vitreous cells, endophthalmitis, vitritis, retinal vasculitis and retinal vein occlusion;
[2]The same patient had both IOI events in this arm.

NGM621 did not cause CNV Conversions[1]

Study Eye CNV Conversions Over 56 Weeks

	NGM621 Q4W (N = 108)	NGM621 Q8W (N = 104)	Sham Pooled (N = 106)
STUDY EYES DEVELOPING CNV (OVERALL)	**3 (2.8%)**	**2 (1.9%)**	**4 (3.7%)**
With Fellow eye CNV at Baseline	1	1	1
With No Fellow eye CNV at Baseline	2	1	3
With Study Eye CNV at Baseline[2]	0	1	0
READING CENTER CONFIRMED CNV CONVERSION	3 (2.8%)	2 (1.9%)	4 (3.7%)

Fellow eye CNV conversion rate was 11 (4.2%) over the course of the study (N= 259)

[1]Events include preferred terms of CNV and neovascular AMD; [2]CNV at baseline in the study eye was identified by an independent retina imaging expert when eye was suspected of CNV conversion and all images were reviewed. CRC = Central Reading Center

CATALINA Phase 2 Trial Topline Readout Conclusions

- CATALINA trial did not meet its primary endpoint
- Pre-specified secondary MMRM analysis showed lesion growth reduction at 24 weeks of 19.8% in the Q4W arm, with a nominal p-value of < 0.05, that diminished at 52 weeks
- Complex and challenging lesions coupled with methodology limitations with FAF grading may have impacted data interpretation
- Post-hoc analyses were employed in attempt to minimize this variability, showing potentially encouraging findings
- NGM621 appeared to have an acceptable safety profile and did not increase CNV conversion
- Additional analyses are ongoing

THANK YOU

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