

Inhibition of Complement C3 in Geographic Atrophy with NGM621: Phase 1 Study Results

Charles Wykoff, MD, PhD

Retina Consultants of Texas and Retina Consultants of America

Financial Disclosures

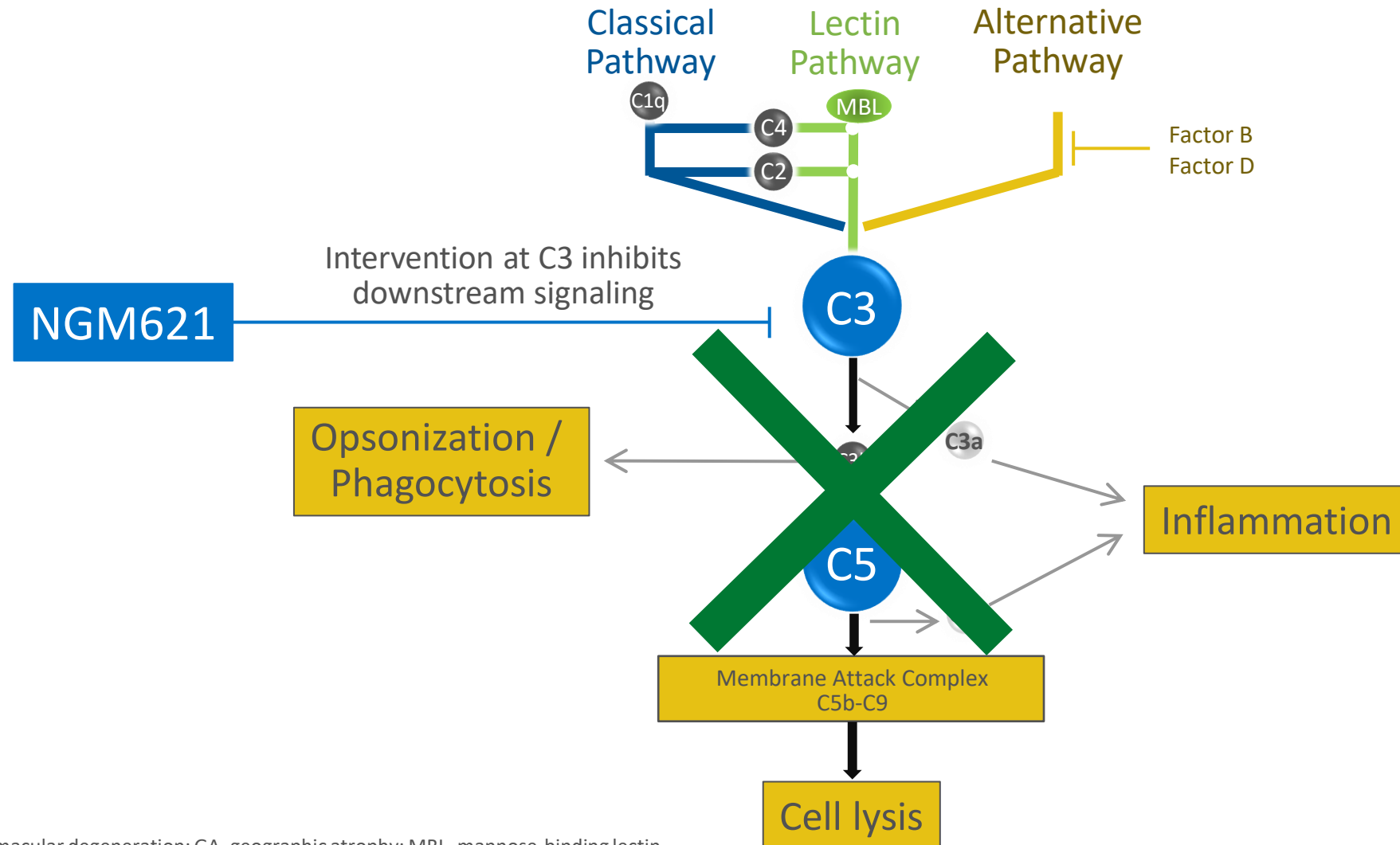
- **C. Wykoff**, Retina Consultants of Texas and Retina Consultants of America. **Disclosures:** Acucela (C), Adverum (C,S), Aerie Pharmaceuticals (S), Aldeyra (S), Alimera Sciences (C), Allegro (C), Allergan (C), Apellis (C,S), Arctic Vision (C), Bausch and Lomb (C), Bayer (C), Chengdu Kanghong Biotechnologies (C,S), Clearside Biomedical (S), DORC (C), EyePoint (C), Gemini Therapeutics (S), Genentech (C,S), Graybug Vision (S), Gyroscope (C), IONIS Pharmaceutical (S), IVERIC Bio (C), Kodiak Sciences (C,S), LMRI (S), Merck (C), Neurotech Pharmaceuticals (S), NGM Biopharmaceuticals (C,S), Novartis (C,S), ONL Therapeutics (C), Opthea (C,S), Outlook Therapeutics (S), Oxurion (C), Palatin (C), Polyphotonix (C), RecensMedical (C,S), Regeneron (C,S), RegenXBio (C,S), Roche (C,S), Samsung Bioepis (S), Santen (S), Senju (S), Taiwan Liposome Company (S), Takeda (C), Thea Open Innovation (C), Xbrane BioPharma (S)

Study Disclosures:

- This study includes research conducted on human subjects
- Institutional Review Board approval was obtained prior to study initiation
- Study funding was provided by NGM Biopharmaceuticals
- Medical writing assistance was provided by ApotheCom (San Francisco, CA, USA) and was funded by NGM Biopharmaceuticals

NGM621 Targets Complement C3, Blocking All Pathways of Complement Activation

- Hypothesis: overactivation of the complement system contributes to AMD pathogenesis, including development & progression of GA

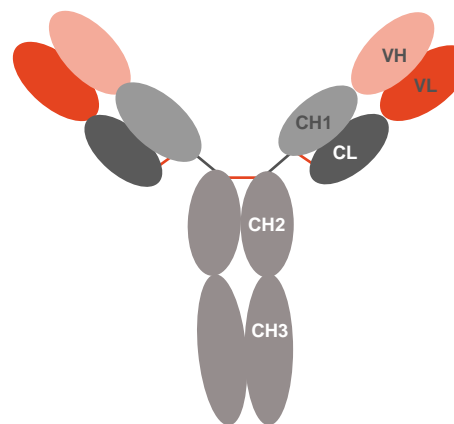


NGM621: A Potent Anti-Complement C3 Antibody

SCIENTIFIC RATIONALE: NGM621 FOR GEOGRAPHIC ATROPHY

- C3 is the most upstream point of convergence for all three complement activation pathways (classical, alt, MBL)
- NGM621 is a potent, long-acting C3 inhibitory monoclonal antibody with the potential to reduce GA progression
- Potential dosing frequency of up to 2 months, without PEGylation

NGM621 MOLECULE ATTRIBUTES



NGM621

Type	Humanized IgG1 monoclonal antibody
Target	Complement C3
MW	~150 kDa
Affinity	$K_D = 340\text{pM}$
Effector Function	Fc mutations eliminating effector function

NGM621 Phase 1: Study Objectives and Key Patient Eligibility Criteria

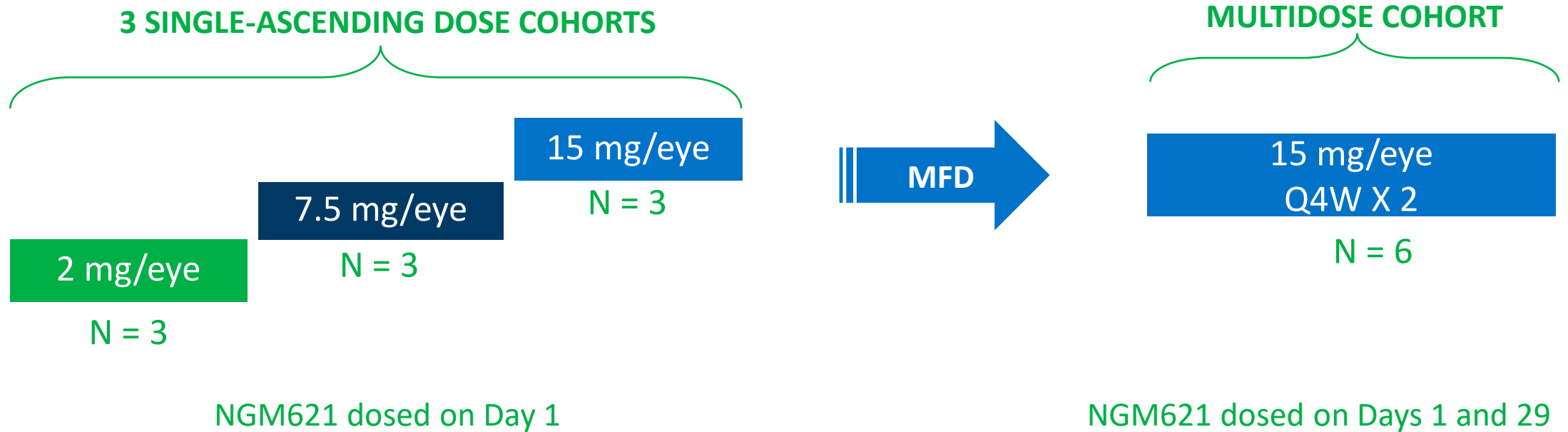
STUDY OBJECTIVES AND ASSESSMENTS

- **Primary:** To evaluate the safety and tolerability of single and multiple IVT injection(s) of NGM621 in patients with GA
- **Secondary:** To characterize the single- and multiple-dose PK of NGM621 and evaluate potential for immunogenicity (serum ADA levels)
- Key Assessments Included:
 - Slit Lamp Biomicroscopy, Fundus Exam
 - Ocular imaging: FAF, CFP, OCT/OCT-A
 - Visual Acuity: ETDRS BCVA & LLVA
 - Vitals / Labs / ECG
 - Serum PK/ADA

PATIENT ELIGIBILITY

- GA secondary to AMD in at least one eye
- ≥ 50 years of age
- GA lesion size in the study eye of $\geq 2.5 \text{ mm}^2$
 - If the GA is multifocal, at least one lesion must be $>1.5 \text{ mm}^2$ with the total lesion size $\geq 2.5 \text{ mm}^2$ on the screening FAF
- ETDRS BCVA between 54 and 4 letters (20/80 to 20/400 Snellen equivalent) in study eye
 - Fellow eye must have BCVA of at least 34 letters (Snellen equivalent 20/200)
- No history or evidence of CNV in either eye (including subclinical neovascular AMD)

NGM621 Phase 1 Study Design



- Patients dosed sequentially; all cohorts followed for 12 weeks (85 days)
- Safety reviews performed after (1) sentinel patient dosed in Cohort 1, and (2) prior to opening enrollment in subsequent cohorts

Phase 1: Patient Demographics and Baseline Characteristics

	SAD Cohort 1 NGM621 2mg (N = 3)	SAD Cohort 2 NGM621 7.5mg (N = 3)	SAD Cohort 3 NGM621 15mg (N = 3)	MD Cohort 4 NGM621 15mg (N=6)	Total (N = 15)
Age, Mean (SD), Years	84.3 (3.06)	79.0 (9.64)	76.7 (4.04)	76.5 (7.04)	78.6 (6.66)
Sex					
Male	100.0%	100.0%	33.3%	33.3%	60.0%
Female	0	0	66.7%	66.7%	40%
Race					
White	100.0%	100.0%	100.0%	100.0%	100.0%
BCVA, Mean (SD) ETDRS letter score	19.3 (16.3)	23.7 (16.1)	36.7 (13.3)	38.8 (12.8)	31.5 (14.7)
Snellen Equivalent	20/400	20/320	20/200	20/160	20/250
GA lesion size, Mean (SD), mm²	5.7 (3)	9.6 (8.5)	21.4 (14.5)	18.7 (11.2)	14.9 (10.8)
Unifocal lesions	66.7%	100%	100%	66.7%	80%
Foveal-involved GA (Yes)	66.7%	100%	100%	83.3%	86.7%

Primary Analysis: Key Safety & Tolerability Observations – Ocular

- No vision-related safety signals detected
- No safety or tolerability signals observed in any cohort
 - No safety events attributed to study drug
 - No endophthalmitis or IOI
 - No cases of CNV in either eye
 - Ocular AEs were representative of those seen with intravitreal injections

SUMMARY OF ADVERSE EVENTS* BY DECREASING FREQUENCY (OCULAR)

	SAD Cohort 1 NGM621 2 mg (N = 3)	SAD Cohort 2 NGM621 7.5 mg (N = 3)	SAD Cohort 3 NGM621 15 mg (N = 3)	MD Cohort 4 NGM621 15 mg (N = 6)	Total (N = 15)
At least one ocular AE	0	1	0	4	5
Conjunctival hemorrhage	0	0	0	3	3
Eye pruritus	0	1	0	1	2

AEs, adverse events; CNV, choroidal neovascularization; IOI, intraocular inflammation; MD, multidose cohort; SAD, single ascending dose cohort.

*Defined as treatment emergent events; includes any events not present prior to initiation of drug treatment or events that were already present with worsened intensity or frequency.

Primary Analysis: Key Safety & Tolerability Observations – Overall

- The maximum evaluated dose, 15 mg, was well tolerated in the single-dose and multidose cohorts
- No safety or tolerability signals observed in any cohort
 - No safety events attributed to study drug
 - No SAEs or deaths

SUMMARY OF ADVERSE EVENTS* BY DECREASING FREQUENCY (NON-OCULAR)

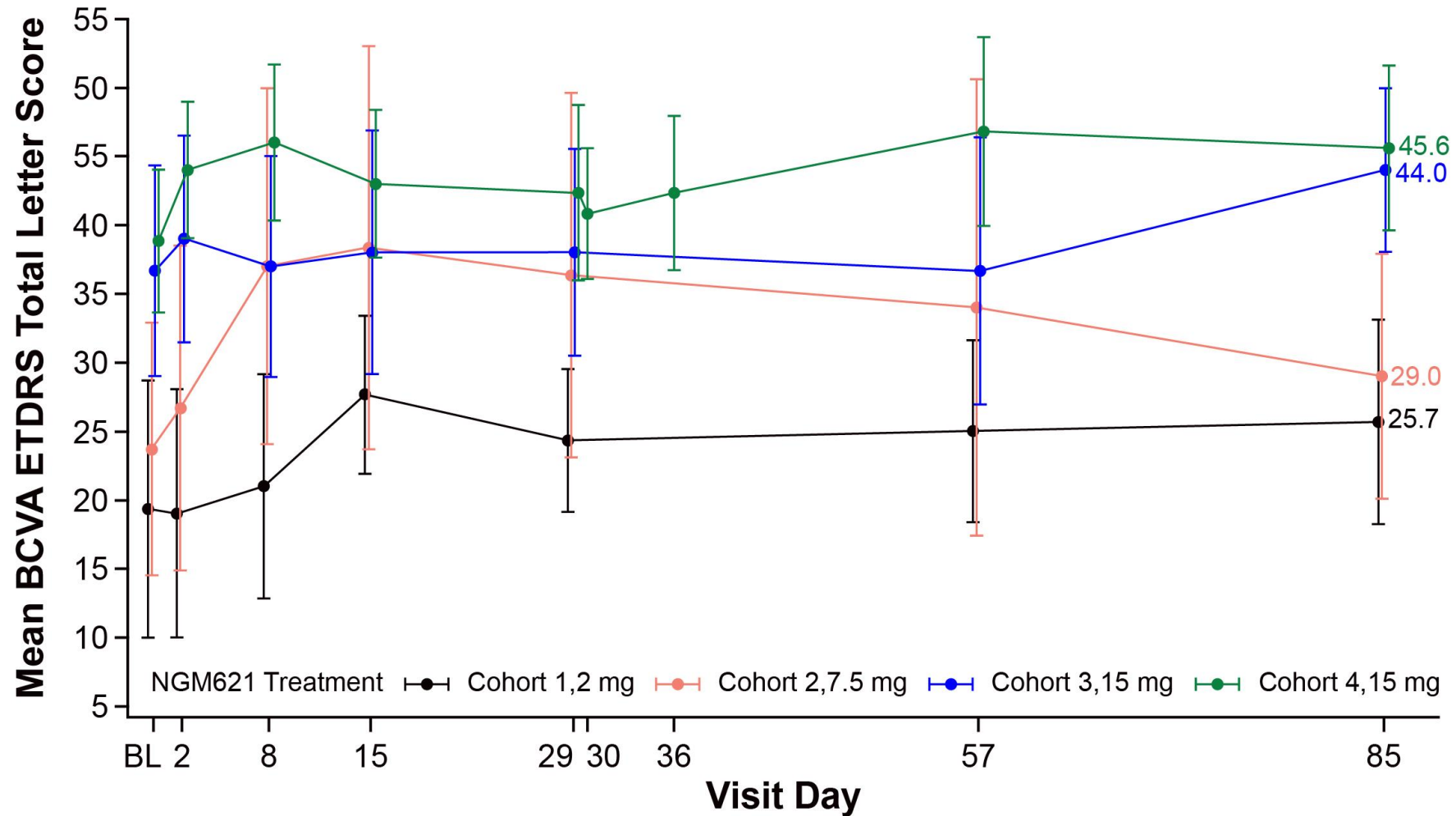
	SAD Cohort 1 NGM621 2 mg (N = 3)	SAD Cohort 2 NGM621 7.5 mg (N = 3)	SAD Cohort 3 NGM621 15 mg (N = 3)	MD Cohort 4 NGM621 15 mg (N = 6)	Total (N = 15)
At least one AE (non-ocular)	3	2	2	2	9
Basal cell carcinoma	1	0	0	0	1
Benign prostatic hyperplasia	1	0	0	0	1
Diarrhea	0	1	0	0	1
Diverticulitis	0	1	0	0	1
Headache	0	0	0	1	1
Hypaesthesia	0	0	0	1	1
Pneumonia	1	0	0	0	1
Sciatica	0	0	1	0	1
Ventricular extrasystoles	0	0	1	0	1

AEs, adverse events; MD, multidose cohort; SAD, single ascending dose cohort; SAEs, serious adverse events.

*Defined as treatment emergent events; includes any events not present prior to initiation of drug treatment or events that were already present with worsened intensity or frequency.

Mean BCVA Was Generally Stable Over the 12-Week Study Duration (Safety Assessment)

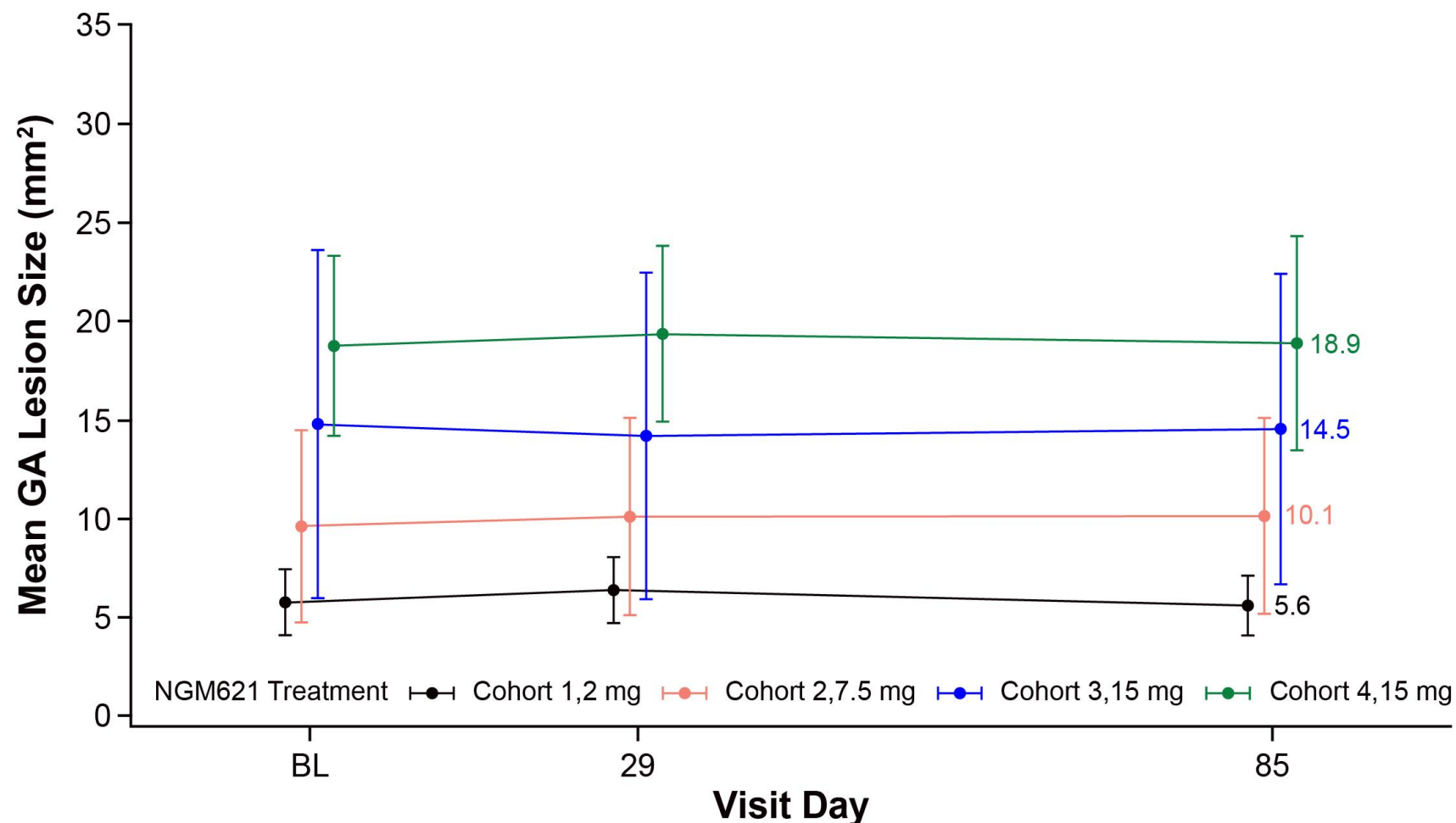
Mean BCVA in ETDRS letter score over time by treatment cohort



BCVA, best corrected visual acuity; BL, baseline.
Error bars represent standard error.

Mean GA Lesion Area Was Generally Stable Over the 12-Week Study Duration

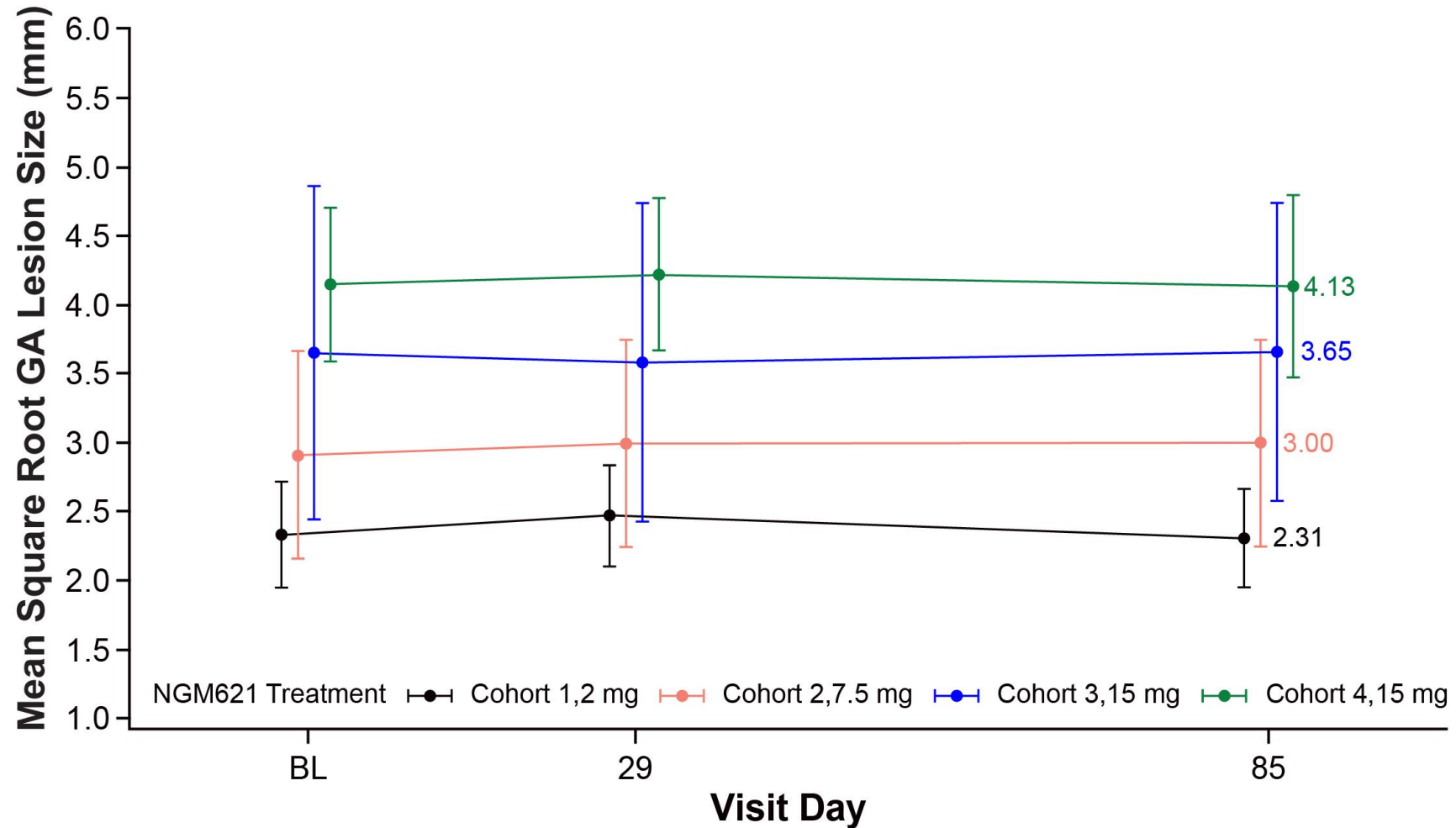
Mean GA lesion size (mm²), as measured by FAF, over time by treatment cohort



BL, baseline; FAF, fundus autofluorescence; GA, geographic atrophy.
Data shown for subjects with at least one post-baseline value. Error bars represent standard error.

Mean GA Lesion Area Was Generally Stable Over the 12-Week Study Duration

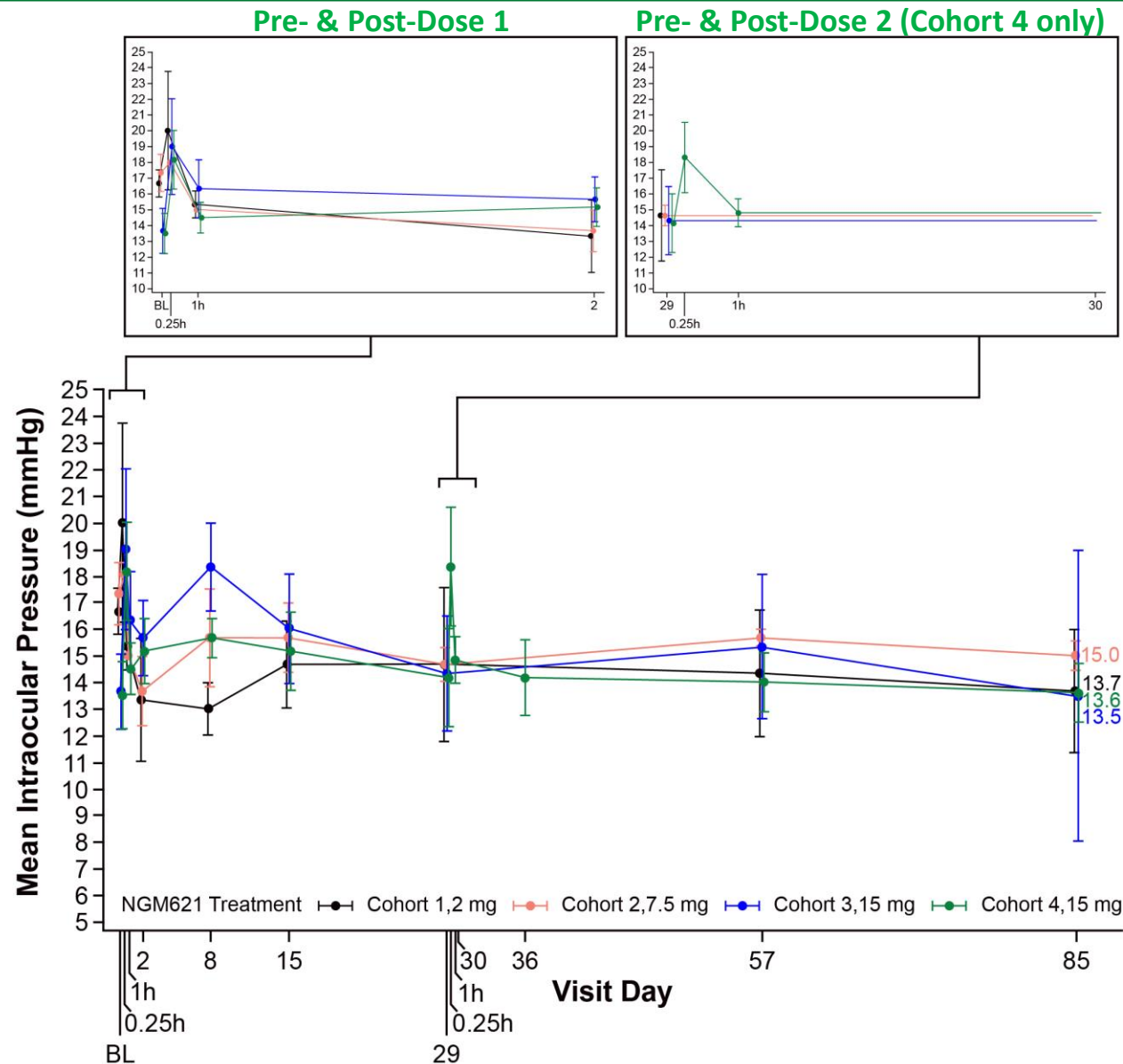
Mean square root GA lesion size (mm), as measured by FAF, over time by treatment cohort



BL, baseline; FAF, fundus autofluorescence; GA, geographic atrophy.
Data shown for subjects with at least one post-baseline value. Error bars represent standard error.

Mean IOP Was Not Meaningfully Impacted Over Time

Mean intraocular pressure (mmHg) over time by treatment cohort

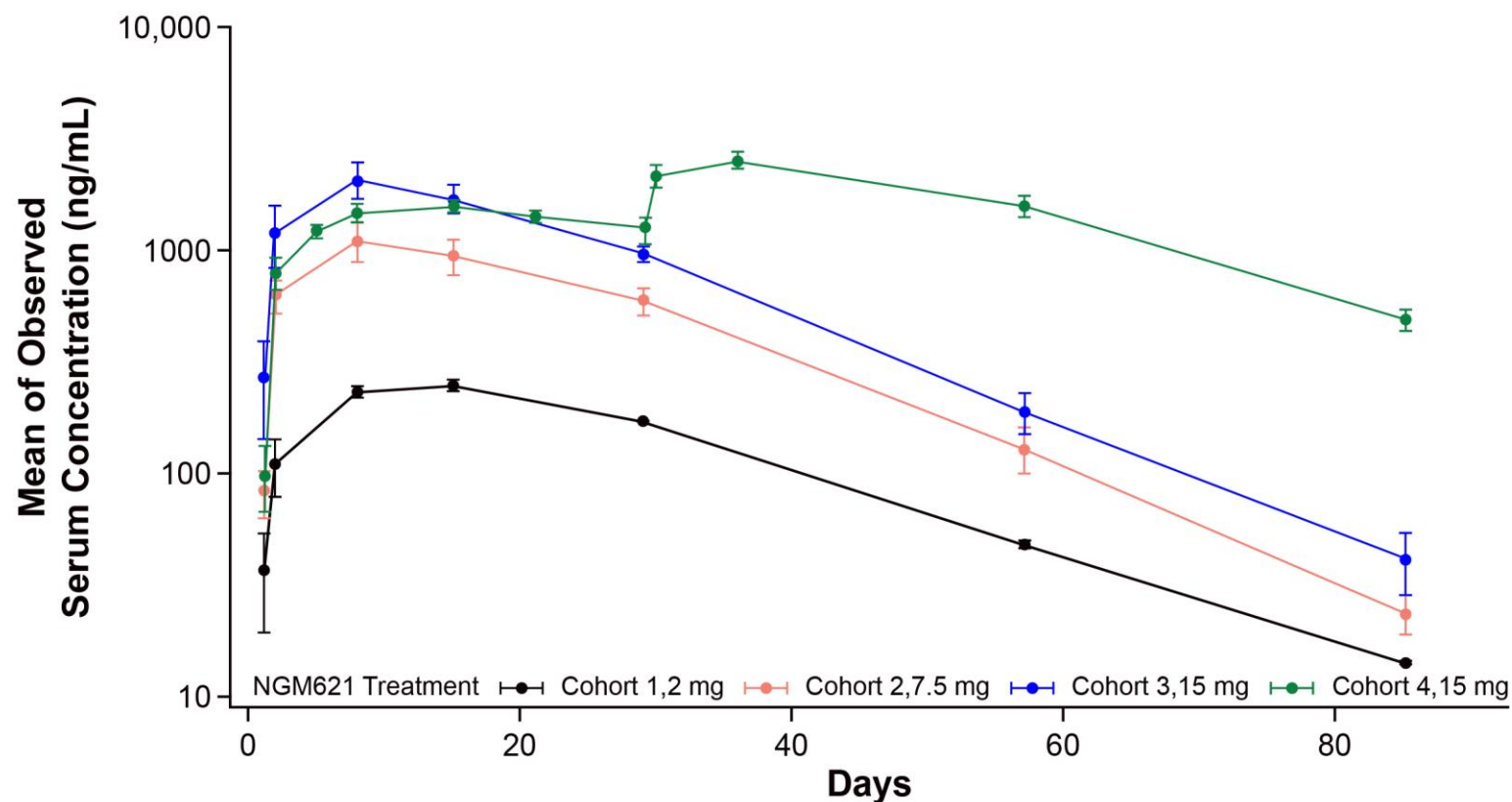


BL, baseline; IOP, intraocular pressure.
Error bars represent standard error.

NGM621 Human Serum PK Profile

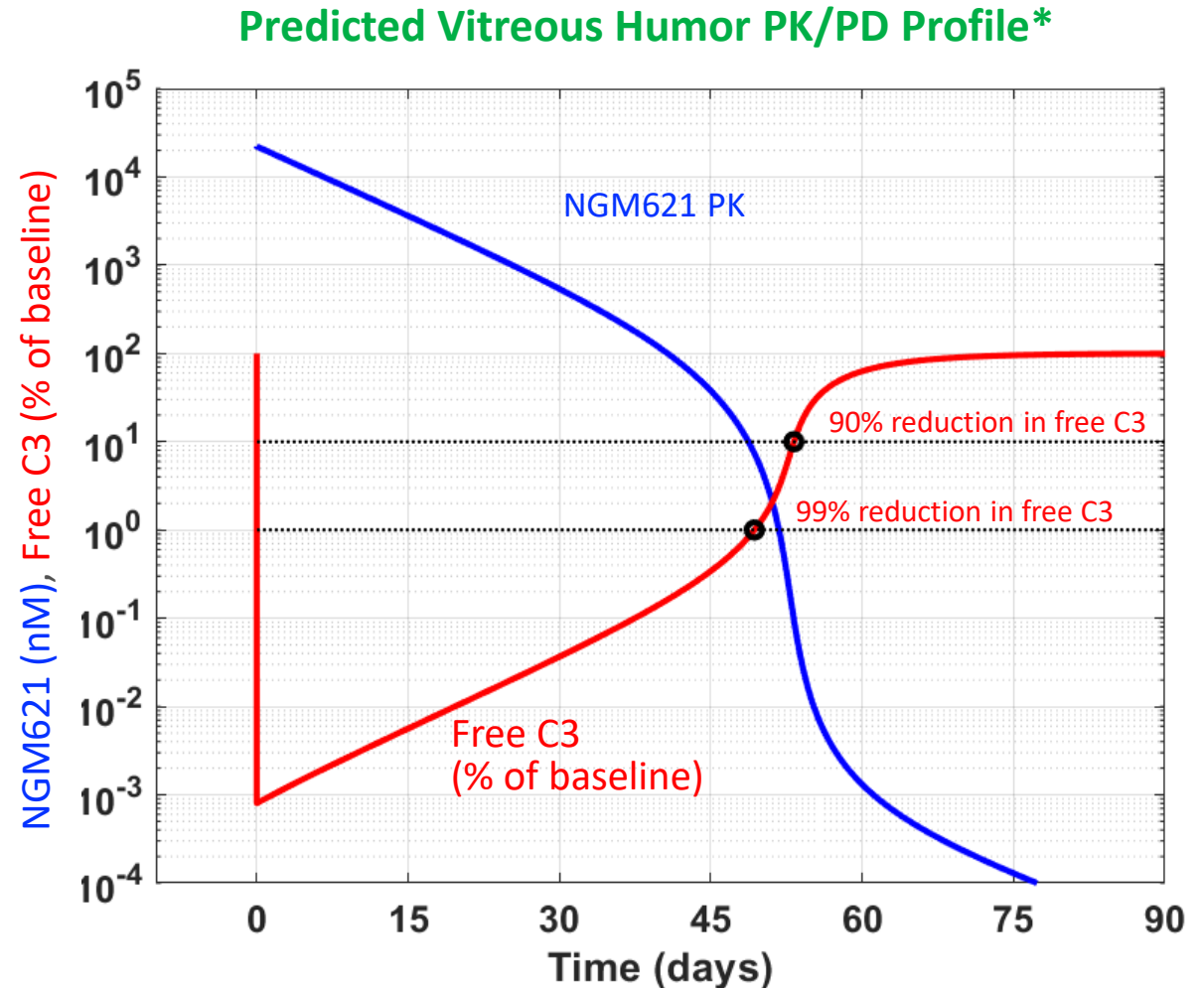
- The serum PK of NGM621 was linear and dose-proportional with low accumulation following every 4-week repeat IVT dosing
- NGM621 serum exposure was below concentrations that produce systemic complement inhibition at the highest IVT dose of 15mg
- All patients were ADA negative at all timepoints

Mean Serum Concentration-time PK Profile post-IVT of NGM621



NGM621 Ocular PK/PD Modeling Supports Every 8-Week IVT Dosing Regimen

- NGM621 is predicted to achieve >90% C3 target engagement in the eye for 7 weeks following a single IVT dose of 15 mg based on a PK/PD model
- PK/PD modeling and simulation support an every 8-week IVT dosing regimen at the 15 mg dose level



IVT, intravitreal; PD, pharmacodynamic; PK pharmacokinetic.

*Ocular PK was not collected in Phase 1; model based on pre-clinical ocular PK data.

Encouraging Phase 1 Results Support Continued Clinical Development of NGM621 for GA

- NGM621 up to 15mg was well tolerated in this first-in-human study
 - All 15 patients enrolled completed the 12-week follow-up
 - No SAEs
 - No drug-related AEs
 - No CNV developed in either eye
- NGM621 serum exposures appeared dose-proportional indicating linear PK in the studied range
 - PK/PD modeling supports NGM621 dose intervals of up to 8 weeks

THANK YOU TO THE NGM621 PHASE 1 STUDY SITES, INVESTIGATORS, AND PATIENTS!

Principal Investigators: Drs. Brian Berger, Tom Chang, David Eichenbaum, Vrinda Hershberger, Charles Wykoff

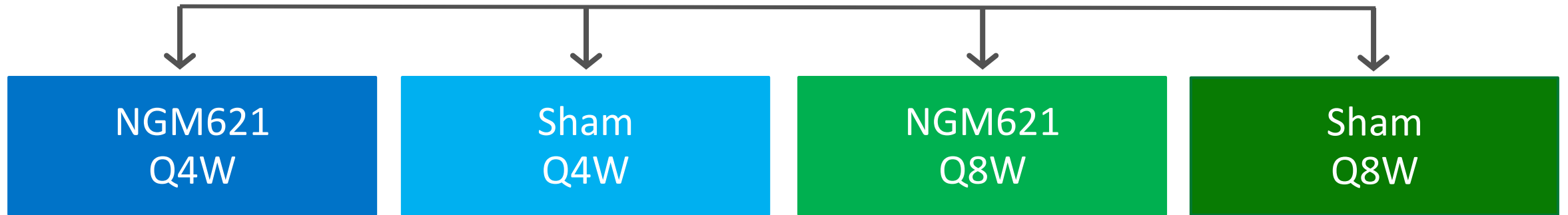
Thank you as well to Alex DePaoli, Husam Younis, Erin Henry, Priya Chandra, Nancy Yuan, Charles Chen and Neang Ly (NGMBio), EyeKor Reading Center, and Harish Shankaran (Merck) for support of the PK/PD modeling work.

Now Recruiting: CATALINA Phase 2 GA Study

Dosing with NGM621 every 4 or 8 weeks vs Sham

PATIENTS WITH GA SECONDARY TO AMD; N = 240¹

Randomized 2:1:2:1



Primary Objective

To evaluate the efficacy and safety after 52 weeks of NGM621 IVT injections administered every 4 or 8 weeks compared to sham control in patients with GA

Design

Phase 2 multicenter, randomized, double-masked, sham-controlled

¹Target enrollment; enrollment ongoing; NCT04465955.

AMD, age-related macular degeneration; GA, geographic atrophy; IVT, intravitreal; Q4, every 4 weeks; Q8, every 8 weeks.