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

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- A. DePaoli, P. Chandra, E. Henry, H. Younis are employees (E) of NGM Biopharmaceuticals, South San Francisco, CA, USA

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

C, consultant/advisor; E, employee; L, lecture fees; O, equity owner; P, patents, royalty; S, grant support.
NGM621: A Potent Anti-Complement C3 Antibody

**NGM621 MOLECULE ATTRIBUTES**

<table>
<thead>
<tr>
<th>Type</th>
<th>Humanized IgG1 monoclonal antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Complement C3</td>
</tr>
<tr>
<td>MW</td>
<td>~150 kDa</td>
</tr>
<tr>
<td>Affinity</td>
<td>$K_d = 340pM$</td>
</tr>
<tr>
<td>Effector Function</td>
<td>Fc mutations eliminating effector function</td>
</tr>
</tbody>
</table>

**SCIENTIFIC RATIONALE: NGM621 FOR GEOGRAPHIC ATROPHY**

- Complement dysregulation is implicated in GA/AMD; C3 is the central convergence point in the complement cascade
- NGM621 is a novel monoclonal antibody that potently inhibits C3, blocking all complement pathways and associated downstream effects, with the potential for extended dosing without PEGylation

AMD, age-related macular degeneration; GA, geographic atrophy; IgG1, immune globulin G1; PEG, polyethylene glycol.
**Phase 1 Study Objectives and Design**

**SINGLE-ASCENDING DOSE COHORTS**
- 2 mg/eye  
  - N = 3
- 7.5 mg/eye  
  - N = 3
- 15 mg/eye  
  - N = 3

**MULTIDOSE COHORT**
- 15 mg/eye  
  - Q4W X 2  
  - N = 6

**STUDY OBJECTIVES**
- **Primary:** To evaluate the safety and tolerability of single and multiple IVT injection(s) of NGM621 in patients with GA
- **Secondary:** To characterize the PK of single or multiple doses of and evaluate immunogenicity of NGM621 (serum ADA levels) NGM621

**COHORT DESIGN**
- 3 Single-Ascending Dose Cohorts of 2mg, 7.5mg, and 15mg
- 1 Multidose Cohort of 15mg NGM621 given twice, 4 weeks apart
- Patients dosed sequentially, followed for 12 weeks
- Safety review performed after sentinel patient dosed and prior to enrollment proceeded to subsequent cohorts

ADA, anti-drug antibodies; GA, geographic atrophy; IVT, intravitreal; MFD, maximum feasible dose; PK, pharmacokinetics; Q4W, every 4 weeks. ClinicalTrials.gov NCT04014777.
Phase 1: Key Patient Eligibility and Assessments

**PATIENT ELIGIBILITY**

- GA secondary to AMD in at least one eye
- ≥50 years of age
- GA lesion size in the study eye of ≥2.5 mm²
  - If the GA is multifocal, at least one lesion must be >1.5 mm² with the total lesion size ≥2.5 mm² 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)

**DOSING AND KEY ASSESSMENTS**

- Cohorts 1-3: Single-Ascending Dose
  - NGM621 dosed on Day 1
- Cohort 4: Multidose
  - NGM621 dosed on Days 1 and 28
- All cohorts were followed for 12 weeks (85 days)
- Key Assessments Included:
  - Slit Lamp Biomicroscopy, Fundus Exam
  - Ocular imaging: FAF, CFP, OCT/OCT-A
  - Visual Acuity: ETDRS BCVA & LLVA
  - Vitals / Labs / ECG
  - Serum / Plasma Samples

AMD, age-related macular degeneration; BCVA, best corrected visual acuity; CFP, color fundus photography; CNV, choroidal neovascularization; ECG, electrocardiogram; FAF, fundus autofluorescence; GA, geographic atrophy; LLVA, low-luminance visual acuity; OCT, optical coherence tomography. ClinicalTrials.gov NCT04014777.
# Phase 1: Patient Demographics and Baseline Characteristics

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

BCVA, best corrected visual acuity; GA, geographic atrophy; MD, multidose cohort; SAD, single ascending dose cohort; SD, standard deviation.
Primary Analysis: Key Safety & Tolerability Observations

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

- No vision-related safety signals detected
  - On average, patients maintained their visual acuity over the 12-week follow-up

### SUMMARY OF ADVERSE EVENTS BY DECREASING FREQUENCY*

<table>
<thead>
<tr>
<th></th>
<th>SAD Cohort 1</th>
<th>SAD Cohort 2</th>
<th>SAD Cohort 3</th>
<th>MD Cohort 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NGM621 2 mg</td>
<td>NGM621 7.5 mg</td>
<td>NGM621 15 mg</td>
<td>NGM621 15 mg</td>
<td></td>
</tr>
<tr>
<td>(N = 3)</td>
<td>(N = 3)</td>
<td>(N = 3)</td>
<td>(N = 6)</td>
<td>(N = 15)</td>
<td></td>
</tr>
<tr>
<td>At least one AE</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Eye pruritus</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Benign prostatic hyperplasia</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Diverticulitis</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Headache</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Hypaesthesia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Pneumonia</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Sciatica</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Ventricular extrasystoles</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

**AEs,** adverse events; **CNV,** choroidal neovascularization; **IOI,** intraocular inflammation; **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 that worsen intensity or frequency.
NGM621 Human Serum PK Profile and Ocular PK/PD Modeling to Support Every 8-Week IVT Dosing Regimen

**PHASE 1 SERUM PK POST-IVT SINGLE & REPEAT DOSING**

- 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 subjects were ADA negative at all timepoints

**OCULAR PK/PD MODELING***

- 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

*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!


Thank you as well to Harish Shankaran (Merck) for support of the PK/PD modeling work and to Neang Ly (NGMBio) for supporting the PK/ADA analyses efforts.

ADA, anti-drug antibodies; AE, adverse events; CNV, choroidal neovascularization; GA, geographic atrophy; PD, pharmacodynamic; PK, pharmacokinetic; SAEs, serious adverse events.
Now Recruiting: CATALINA Phase 2 GA Study
Dosing with NGM621 every 4 or 8 weeks vs Sham

PATIENTS WITH GA SECONDARY TO AMD; N = 240

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

Design
Phase 2 Multicenter, Randomized, Double-Masked, Sham-Controlled

NGM621 Q4W  Sham Q4W  NGM621 Q8W  Sham Q8W

Randomized 2:1:2:1

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

1 Target enrollment; enrollment ongoing NCT04465955.