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Low-Dose AAV Gene Therapy NG101 for Wet AMD: Preclinical Results and Ongoing Phase 1/2a Trial Design

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Purpose

Wet age-related macular degeneration (wAMD) remains a major cause of vision loss despite current anti-VEGF therapies. NG101, an AAV8 vector-based gene therapy encoding aflibercept, is being developed as a single administration treatment for wAMD. Using the proprietary CAT311 promoter, NG101 aims to achieve robust and sustained aflibercept expression at significantly lower doses than other AAV-based wAMD gene therapies in development. Here, we present NG101's preclinical efficacy, safety, and the ongoing Phase 1/2a trial design.

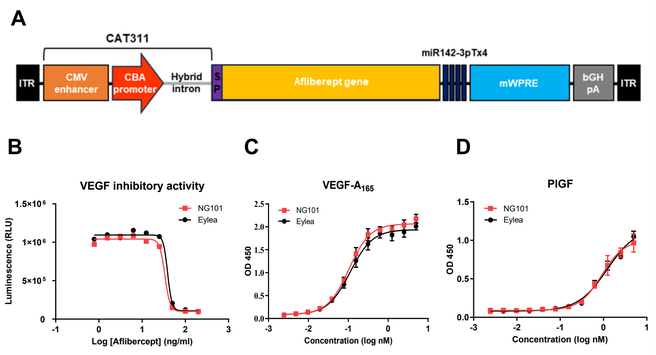
Results

Preclinical data demonstrated that NG101 effectively reduced CNV lesion leakage and size in NHPs. At 3×10^9 vg/eye, NG101 showed comparable efficacy to Eylea (aflibercept) in suppressing CNV formation. Sustained aflibercept expression was observed in ocular tissues for up to 1 year post-injection, with only mild and transient ocular inflammation. Based on these results, a Phase 1/2a clinical trial is underway to further evaluate NG101 as a low-dose gene therapy for wAMD.

Methods

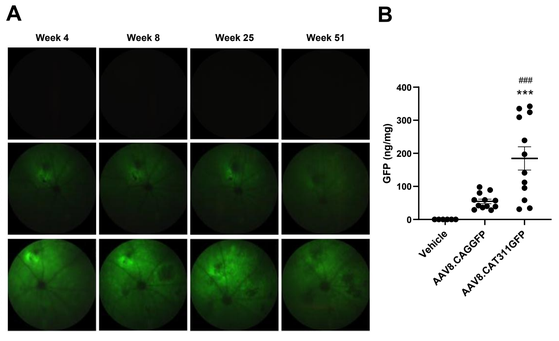
- Preclinical: The efficacy of NG101 was evaluated in a laser-induced choroidal neovascularization (CNV) model in non-human primates (NHPs). CNV was induced 56 days post-administration. Lesion leakage and size were assessed via fluorescein angiography (FA) and optical coherence tomography (OCT). Safety assessments included slit-lamp biomicroscopy, intraocular pressure measurements, and electroretinography.
- Clinical trial design: The ongoing Phase 1/2a trial (NCT05984927) is a multicenter, open-label, dose-escalation study enrolling 18 wAMD patients across 3 cohorts (n=6 each) receiving 1×10^9, 3×10^9, and 8×10^9 vg/eye. Inclusion criteria include active CNV secondary to wAMD, documented anti-VEGF response, and BCVA 20/40-20/400. NG101 is administered via subretinal injection. The primary endpoint is safety and tolerability at 24 weeks. Secondary endpoints include aflibercept expression, CNV activity, central subfield thickness, BCVA, and rescue injections.

Figure 1. Aflibercept produced by NG101 binds to and inhibits VEGF signaling comparable to Eylea in vitro



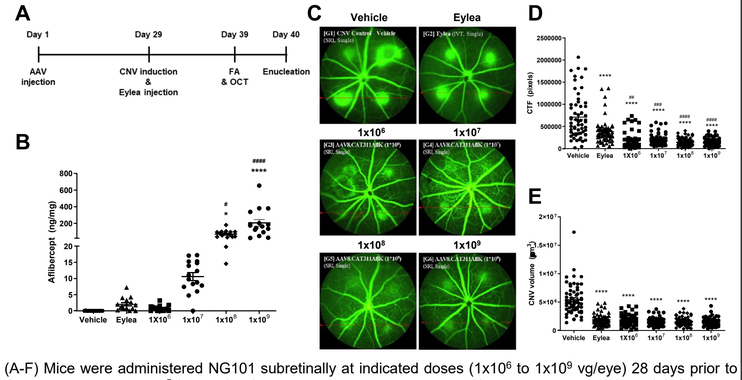
(A) Graphical scheme of aflibercept expression cassette of NG101. (B) The VEGF inhibitory activities of aflibercept produced by NG101 and Eylea® were evaluated. (C and D) The binding selectivity of aflibercept produced by NG101 and Eylea® to recombinant VEGF-A_{165} (C) and placental growth factor (PIGF) (D) were evaluated. RLU: relative luminescence unit. OD450: optical density at absorbance 450nm.

Figure 2. CAT311 promoter drives robust and durable ocular gene expression in mice.



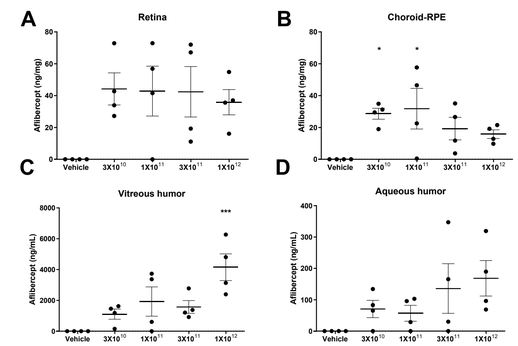
(A and B) Fifty-one weeks after a single subretinal injection of either AAV8.CAGGFP or AAV8.CAT311GFP at a dose of $5x10^8$ vg/eye, GFP expression was evaluated. (A) Representative fundus images are shown. (B) The GFP expression levels were measured. Data are shown as mean ± SEM. (B) Statistical analysis: One-way ANOVA. ***p<0.001 versus Vehicle and ###p<0.01 versus AAV8.CAGGFP.

Figure 3. NG101 administration prevents laser-induced CNV formation in mice



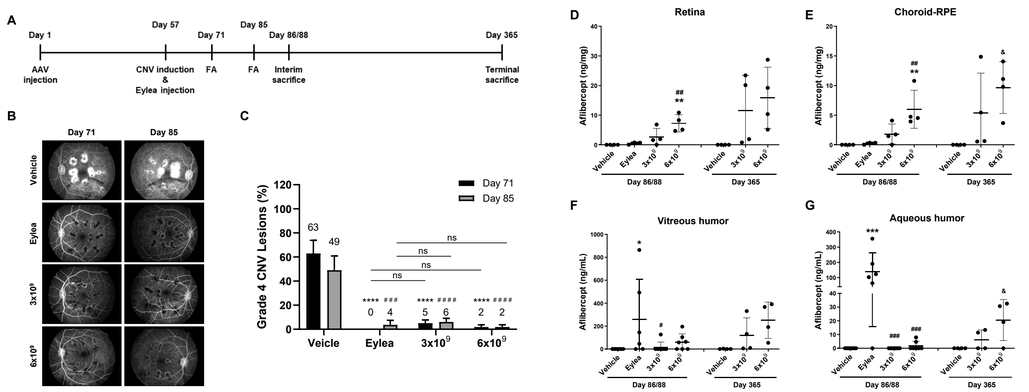
(A-F) Mice were administered NG101 subretinally at indicated doses ($1x10^6$ to $1x10^9$ vg/eye) 28 days prior to CNV induction, or Eylea® (40 μg/eye) intravitreally once immediately after the induction of CNV. (A) Overview of efficacy testing in the mouse model of laser-induced CNV. (B) Ten days post CNV induction, aflibercept expression was measured. Data are shown as mean ± SEM. (C) Representative fluorescein angiography (FA) images are shown. (D) The CNV lesion leakage was evaluated. Data are shown as mean ± SEM. (E) The volume of CNV lesions based on optical coherence tomography (OCT) images was measured. Data are shown as mean ± SEM. (B, D and E) Statistical analysis: One-way ANOVA. *P<0.05 ****P<0.0001 versus Vehicle and #P<0.05, ##p<0.01, ###P<0.001, ####p<0.0001 versus Eylea®. CTF: corrected total fluorescence.

Figure 4. High levels of aflibercept accumulate in the retinal region following a single subretinal administration of NG101 in NHPs.



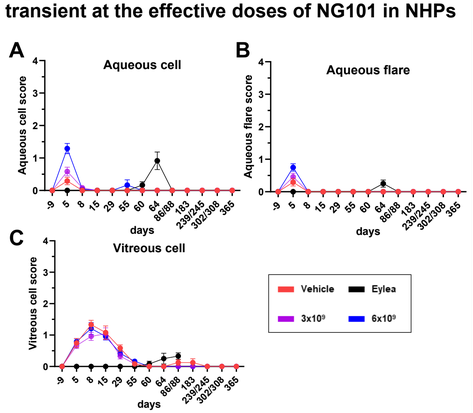
(A-D) Cynomolgus monkeys were administered Vehicle or NG101 at indicated doses ($3x10^{10}$ to $1x10^{12}$ vg/eye) via bilateral subretinal injection. Fifty-seven days post-injection, all animals were euthanized, and aflibercept concentrations were measured in the retina (A), choroid-RPE (B), vitreous humor (C) and aqueous humor (D). Data are shown as mean ± SEM. (A-D) Statistical analysis: One-way ANOVA. *P<0.05, ***P<0.001 versus Vehicle.

Figure 5. Subretinally administered of NG101 effectively suppresses CNV formation at low doses in NHPs



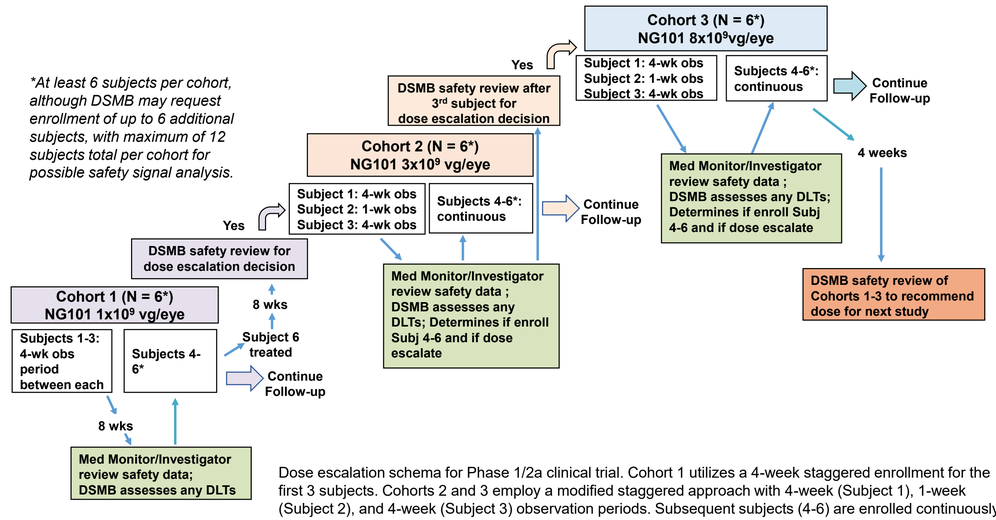
(A-G) NG101 was administered subretinally at indicated doses ($3x10^9$ or $6x10^9$ vg/eye) and Eylea® (2 mg/eye) was injected intravitreally in cynomolgus monkeys. (A) Overview of efficacy testing in NHP CNV model. (B) Representative fluorescein angiography (FA) images are shown. (C) The percentage of grade 4 CNV lesions was evaluated. Data are shown as mean ± SEM. (D-G) Aflibercept expression levels in the retina (D), choroid-RPE (E), vitreous humor (F), and aqueous humor (G) were measured at day 86/88. Additionally, two animals (one male and one female) from Vehicle, $3x10^9$, and $6x10^9$ dose groups were followed up until day 365. Data are shown as mean ± SEM. (C-G) Statistical analysis: (C) Two-way ANOVA. ****0.0001 versus Vehicle on day 71 and ###p<0.001, ####p<0.0001 versus Vehicle on day 85. (D-G) Statistical analysis: One-way ANOVA. *P<0.05, **P<0.01, ***P<0.001 versus Vehicle on day 86/88, #P<0.05, ##P<0.01, ###P<0.001 versus Eylea® on day 86/88, &P<0.05 versus Vehicle on day 365, and @P<0.05, @@@P<0.001 versus $3x10^9$ on day 86/88.

Figure 6. Ocular inflammation was mild and transient at the effective doses of NG101 in NHPs



(A-C) Ophthalmic examinations were conducted on the same animals described in Figure 5 to assess ocular inflammatory responses. Parameters evaluated included aqueous cell (A), aqueous flare (B), and vitreous cells (C), monitored up to day 86/88. Additionally, two animals (one male and one female) from each of the Vehicle, $3x10^9$, and $6x10^9$ vg/eye groups were followed up until day 365. Data are shown as mean ± SEM.

Figure 7. Dose Escalation Schema for Clinical trial Phase 1/2a



Dose escalation schema for Phase 1/2a clinical trial. Cohort 1 utilizes a 4-week staggered enrollment for the first 3 subjects. Cohorts 2 and 3 employ a modified staggered approach with 4-week (Subject 1), 1-week (Subject 2), and 4-week (Subject 3) observation periods. Subsequent subjects (4-6) are enrolled continuously if no DLTs are observed. DSMB reviews safety data for dose escalation decisions.

Conclusions

- By leveraging its proprietary vector design, NG101 may offer robust efficacy and safety at lower vector doses than other gene therapies for wAMD.
- NG101 has the potential to address challenges associated with current anti-VEGF therapy, such as the burden of frequent injections.
- The ongoing Phase 1/2a trial will provide critical insights into the safety, tolerability, and initial efficacy in wAMD patients.

References

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