Six-Month First-in-Human Safety and Efficacy Data of Subretinal NG101 – A Novel Low-Dose AAV Gene Therapy for Wet AMD

Phase 1/2a Open-label and Dose-escalation Study: NG101WA-01

58th Annual Scientific Meeting of the Retina Society

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Reporting for the SENSE Study Group

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Avastin, Kenalog, Methotrexate, and GoreTex are not FDA approved for intraocular use.

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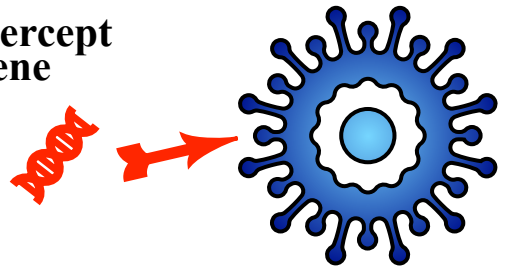
SENSE Study (NG101WA-01)

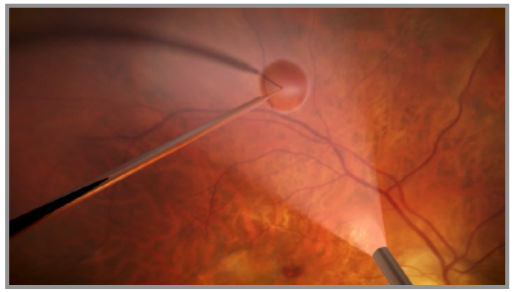
Key Features of NG101

Aflibercept gene

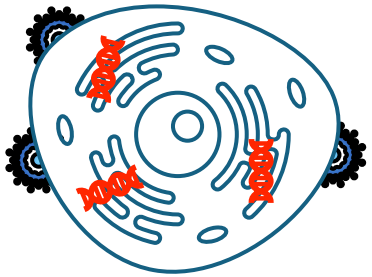


AAV8 vector, proprietary CAT311 promoter

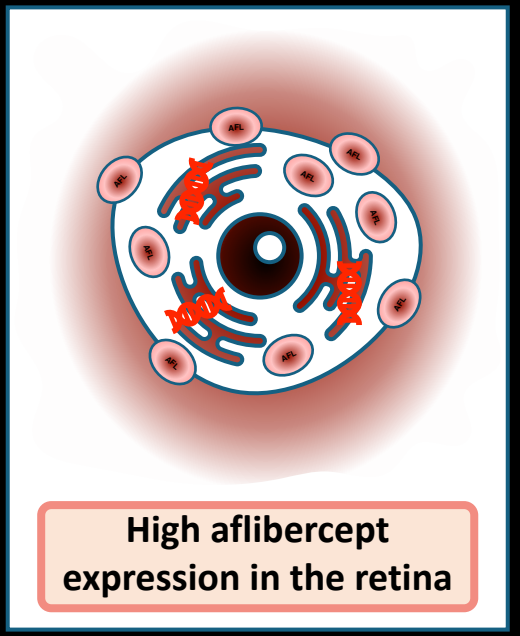
Designed for strong Anti-VEGF protein expression



Administration of NG101 via subretinal injection



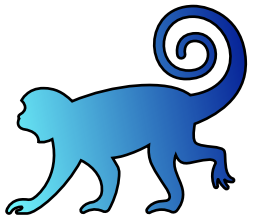
Transfection of retinal cells



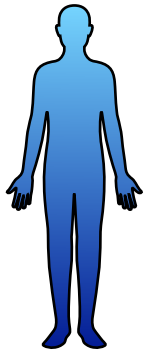
High aflibercept expression in the retina

Therapeutic effect at low dose

CNV lesions of clinical significance (Grade IV) in NHP CNV model



First in Human SENSE Study (NG101WA-01)



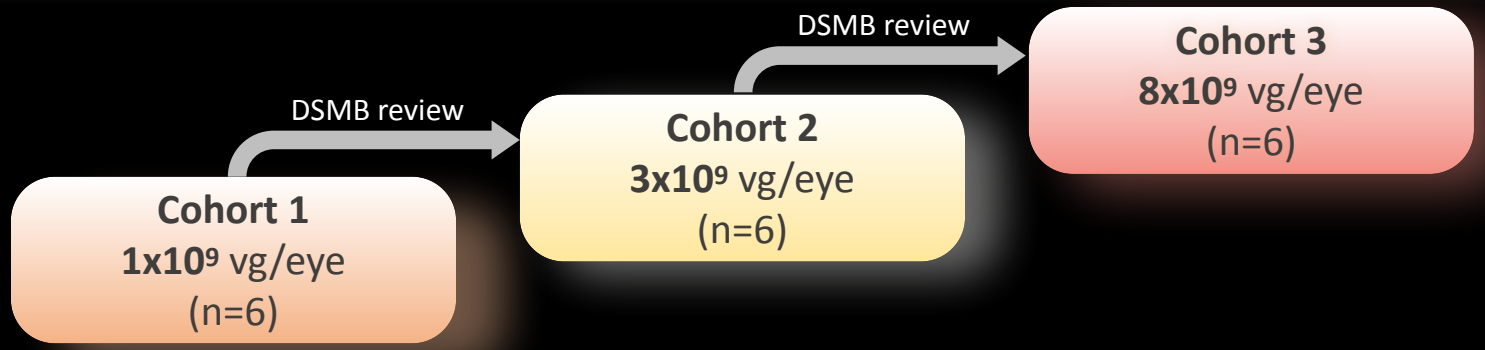
* SENSE: A Phase 1/2a Open-label Study to Evaluate Safety, Tolerability, and Preliminary Efficacy of NG101 AAV Gene Therapy in Subjects with WEt Age-Related Macular Degeneration

ITR: Inverted Terminal Repeat, NHP: Non-Human Primate. IVT: Intravitreal injection, SRI: subretinal injection

SENSE Study (NG101WA-01)

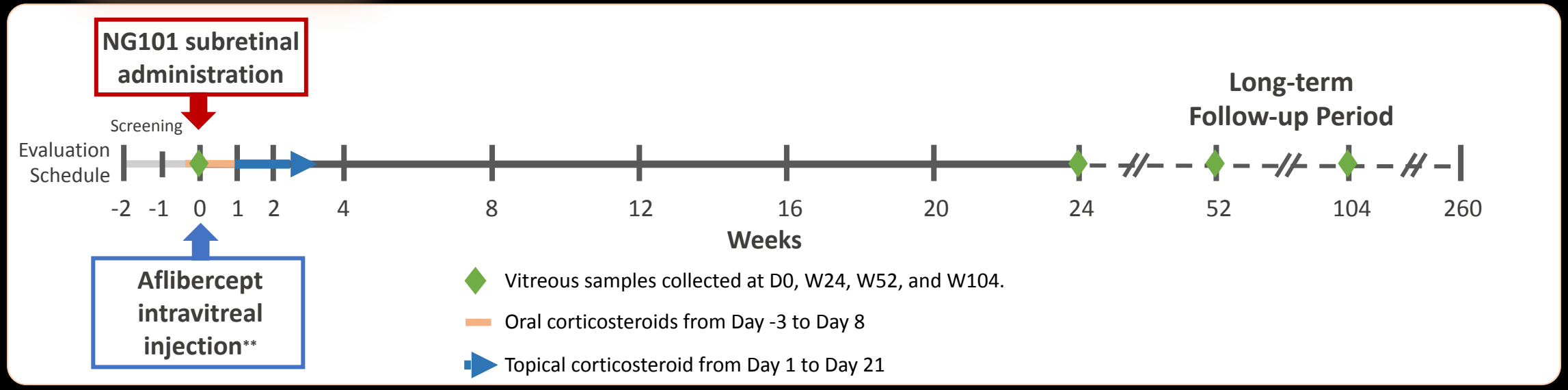
Phase 1 Study Design and Current Status

Key End Points: Evaluate Safety, Tolerability, and Efficacy



Current Status of the Study

- **Cohort 1:** 24-Week Safety and Efficacy
- **Cohort 2:** Preliminary Safety
- **Cohort 3:** Actively enrolling - no data yet



* Approved by Health Canada and FDA (**NCT05984927**)

**Aflibercept is administered to provide therapeutic coverage during the onset of NG101-mediated transgene expression.

SENSE Study (NG101WA-01)

Key Eligibility Criteria and Endpoints

Key Inclusion Criteria	• Age: 50 to 89 years old • Choroidal Neovascularization (CNV) due to wet Age-related Macular Degeneration (wAMD) • Best Corrected Visual Acuity (BCVA) between 70 (20/40) and 20 (20/400) ETDRS letters • At least 3 anti-VEGF injections in the past 6 months
Primary Endpoint (Safety)	• Incidence and severity of ocular and non-ocular adverse effects (week 24)
Secondary Endpoints (Safety and Efficacy)	• Incidence and severity of ocular and non-ocular adverse side effects through week 260 • Rescue retreatments • Change in Best Corrected Visual Acuity (BCVA) • Changes in Central Subfield Thickness (CST) • Change in immunogenic responses in serum • Changes in Choroidal Neovascularization (CNV) activity markers

SENSE Study (NG101WA-01)

Rescue Criteria (Ranibizumab or Faricimab) After Week 4:

- OCT central subfield thickness (CST) increase ≥100 µm* from active CNV, regardless of visual acuity.
- BCVA loss >10 ETDRS letters* with intraretinal or subretinal fluid on OCT from active CNV.
- New subretinal hemorrhage, intraretinal hemorrhage, or lipid exudation observed on clinical examination or fundus photography attributable to active CNV.
- At the investigator’s discretion for the subject's safety.

* From baseline of Day -7

SENSE Study (NG101WA-01)

RESULTS: Cohort 1 Patient Baseline Charachteristics

	Patient 1	*Patient 2*	*Patient 3*	*Patient 4*	*Patient 5*	*Patient 6*	Average
Age (years)	78	80	73	66	80	77	**76**
Gender / Race	Male / Caucasian	Female / Caucasian	Female / Asian	Female / Caucasian	Female / Caucasian	Female / Caucasian	-
BCVA (EDTRS letters)	47	56	47	72	65	57	**57**
CST (microns)	267	305	390	295	254	256	**295**
Time since Diagnosis (years)	8	4	11	9	4	15	**9**
Number of Anti-VEGF Injections (1 year prior to NG101 injection)*	10	10	8	13	9	9	**9.8**

* Number of anti-VEGF injections before screening

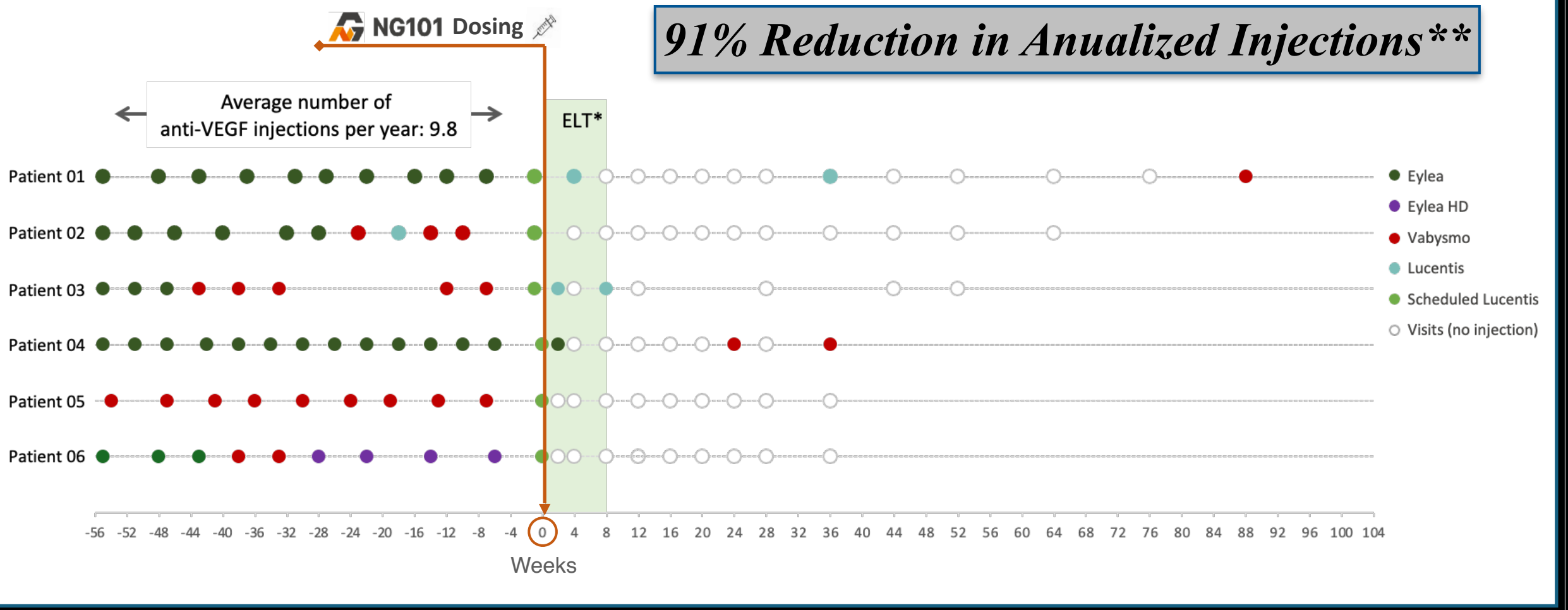
SENSE Study (NG101WA-01)

RESULTS: Favorable Safety and Tolerability Profile to Date - Cohorts 1 and 2

- NG101 continues to be generally well-tolerated across all subjects (n=12) who have been enrolled and dosed through Cohort 2.
- No NG101-related serious adverse events (SAEs) or dose-limiting toxicities (DLTs).
- No NG101-related clinically significant RPE changes or retinal degeneration.
- No cases of hypotony, vascular occlusions, endophthalmitis, vasculitis, or retinitis.

SENSE Study (NG101WA-01)

RESULTS: Robust Treatment Burden Reduction in Cohort 1



Data Cutoff: 25 Aug 2025

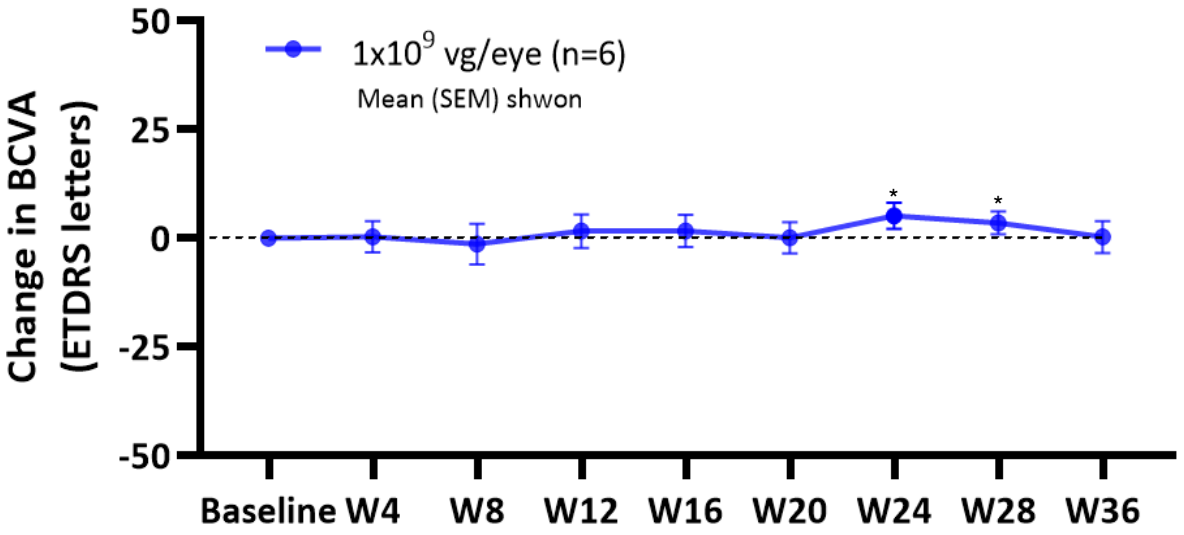
*ELT (Expression Lag Time): Period required for the AAV8 vector to transduce target cells and for the transgene (NG101) to be expressed. Based on our non-clinical data, the ELT is estimated to be approximately 8 weeks.

**The annualized reduction rate was calculated based on the total number of anti-VEGF injections during the baseline period (12 months prior to treatment) versus the total number during the study period. For this analysis, the initial 4-week observation period was excluded, and only injections administered from Week 8 onwards were included in the post-treatment count.

SENSE Study (NG101WA-01)

Efficacy: BCVA and OCT-CST

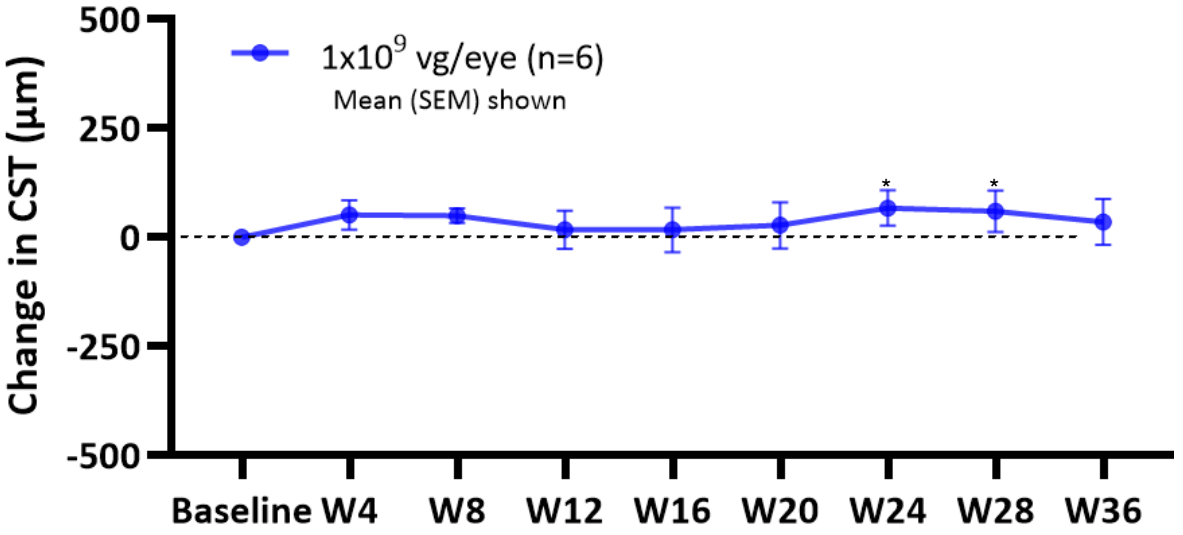
Best Corrected Visual Acuity (BCVA)



Mean BCVA change from baseline to W36

0 letter

Central Subfield Thickness (CST)



Mean CST change from baseline to W36

+36 µm

* n=5 due to one subject's missed visit.

SENSE Study (NG101WA-01)

Vitreous Aflibercept Concentration (n = 7) at Weeks 0, 12*, 24 and 52

- All vitreous levels of NG101 Transgene Protein (aflibercept) were below the 4 ng/mL Lower Limit of Quantification (LLOQ).
- Non-Human Primate data demonstrated that aflibercept was present in high concentrations in the retina with efficacy in inhibiting CNV despite not being detectable in the vitreous.
- Unlike intravitreal aflibercept injection, NG101 directly delivers aflibercept to the retina and RPE.
- The vitreous concentration of Transgene Protein associated with therapeutic efficacy after subretinal NG101 remains unknown
- Very low vitreous Transgene Protein levels may have positive systemic safety implications for NG101 and possibly other subretinal therapies.

*A few vitreous samples were collected at Week 12 under a prior protocol.

SENSE Study (NG101WA-01)

NG101 vs Leading Gene Therapies

Drug	NG101	RGX-314		4D-150	ADVM-022
Company	Neuracle Genetics	REGENXBIO™		4DMT	ADVERUM
Transgene	**Aflibercept**	Ranibizumab-like Fab		Aflibercept and RNAi	Aflibercept
Promoter	**CAT311**	CAG		CAG	CMV
AAV	**AAV8**	AAV8		R100	AAV.7m8
Delivery (volume)	**Subretinal (100µl)**	Subretinal (250µl)	Suprachoroidal (100 - 200µl)	Intravitreal	Intravitreal
Stage	**Phase 1/2a**	Phase 3	Phase 2	Phase 3	Phase 3
Dose (vg/eye)	**1×10^9** **3×10^9** **8×10^9**	6.4×10^{10} 1.3×10^{11}	2.5×10^{11} 5×10^{11} 1×10^{12}	3×10^{10}	6×10^{10}

NG101 → **Low Effective Dose** → **Favorable Safety Profile**

SENSE Study (NG101WA-01)

Conclusions

- ***Safety***
  - NG101 has been well-tolerated by all Cohort 1 and 2 patients to date.
- ***Efficacy***
  - A single injection of subretinal NG101 ($1x10^9$ vg/eye in 100 µL) led to a 91% reduction in the annualized rate of anti-VEGF injections in Cohort 1
  - BCVA and OCT-CST remained stable in Cohort 1 subjects.
- ***Next Steps***
  - Enrollment for Cohort 3 (high dose: $8x10^9$ vg/eye).
  - Phase 2b study design
  - BD discussions (contact BD@neuraclegen.com)

SENSE Study (NG101WA-01)

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  - Robert A Sisk, MD
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  - Netan Chaudhry, MD
  - Eduardo V Navajas, MD
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- OIRRC, Independent Reading Center
- Neuracle Genetics Research & Development Team

Thank You ! ! !

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