Interim Subretinal Gene Therapy Safety Results in Two Phase 1/2 Open-label, Dose-escalation Clinical Trials to Treat Achromatopsia

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Achromatopsia (ACHM)

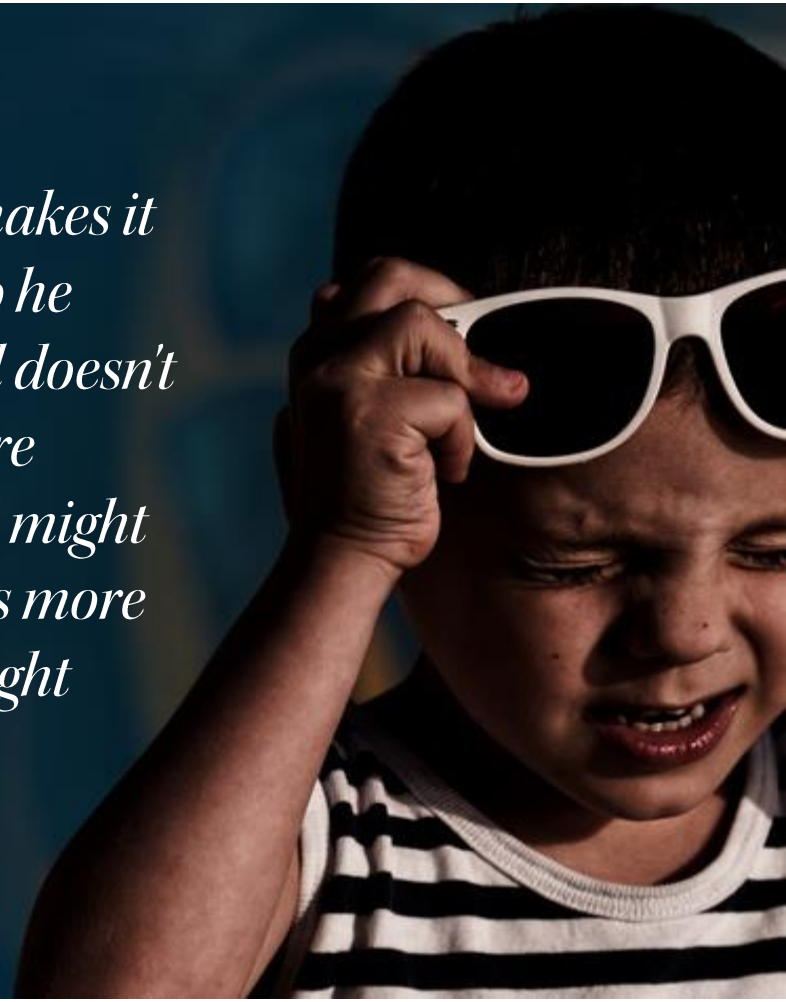
OVERVIEW

- Approximately 27,000 patients in US and EU affected
- AGTC focused on A3 and B3 gene mutations
  - B3 accounts for approximately 50% or 14,000 patients
  - A3 accounts for approximately 25% or 7,000 patients
- Severely impaired vision and day blindness due to loss of cone photoreceptor function
- No current treatments

IMPACT

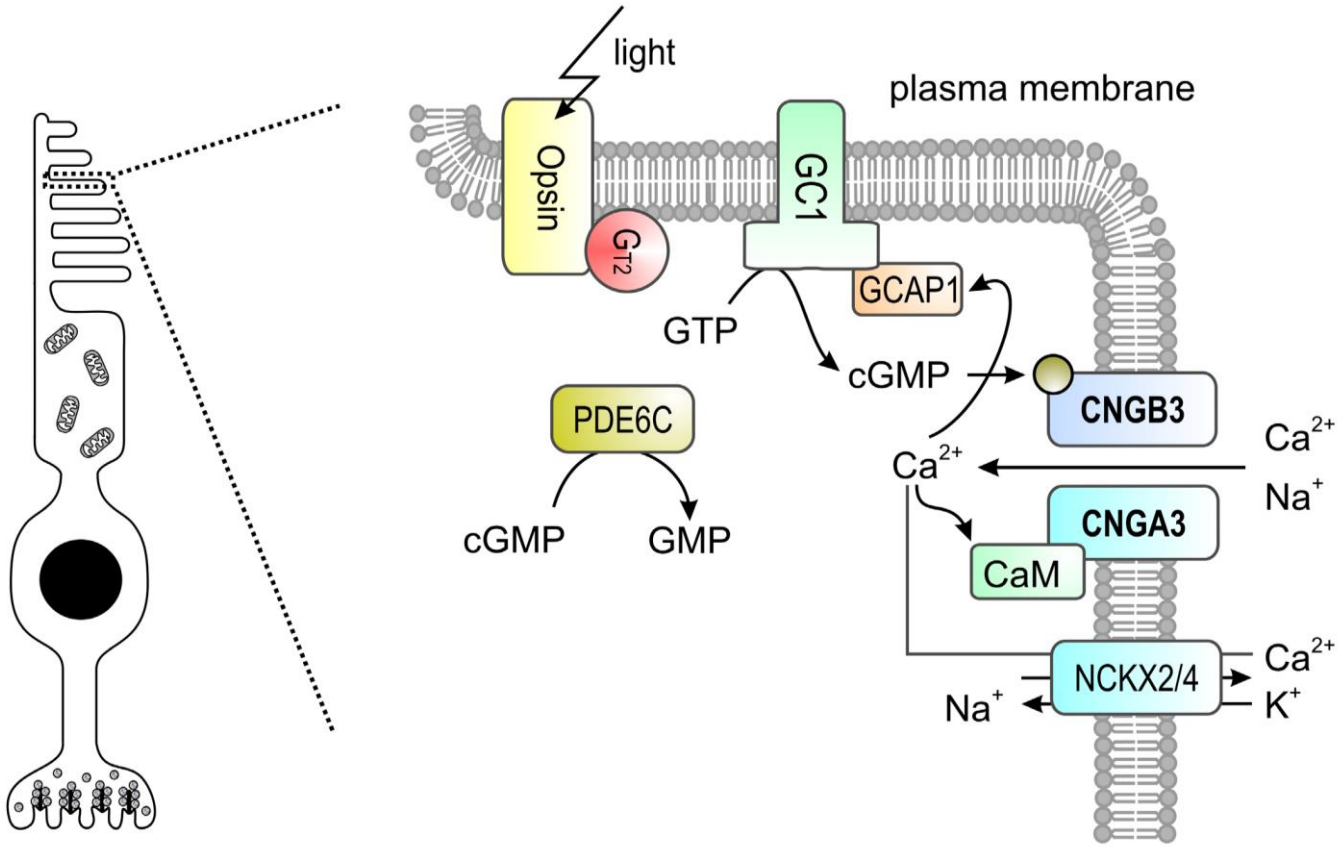
- Extremely poor vision, legally blind
- Extreme light sensitivity (day blind)
- Complete loss of color discrimination

"The bright light makes it really hard for him, so he tends to freeze up and doesn't want to walk anywhere because he's afraid he might injure himself. He gets more cautious in new or bright environments."



Causes of ACHM

- Mutations in two genes, CNGA3 (A3) and CNGB3 (B3), account for 75% of cases
  - CNGB3 mutations in 50%, CNGA3 mutations in 25% of cases
- Both genes encode subunits of cone cGMP-gated ion channels
- Essential to phototransduction cascade

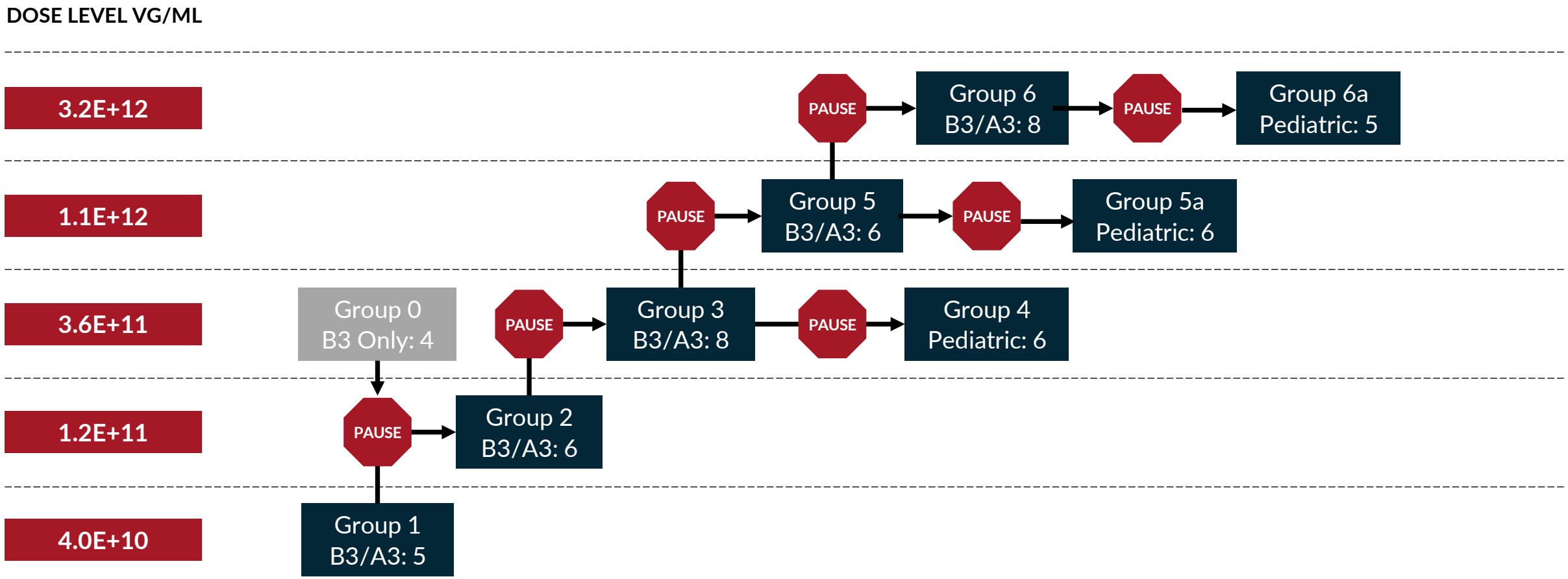


AGTC 401 and AGTC 402: Primary Objective & Key Endpoints

- Primary Objective: To evaluate the safety of AGTC-401 (B3) and AGTC-402 (A3) administered by subretinal injection in patients with achromatopsia

- Primary Endpoint: Safety
- Key Secondary Endpoints:
  - Visual Sensitivity as measured by static perimetry
  - Light Discomfort as measured by Ocular Photosensitivity Analyzer (OPA)
  - Best Corrected Visual Acuity (BCVA) as measured by Early Treatment Diabetic Retinopathy Study (ETDRS)

ACHM Trial Overview: Dose Escalation and Age De-escalation



Expanded Groups 4a (A3), 5a (B3) and 6a (A3 & B3) to enroll pediatric patients 4-8 years of age

Total N=24 for A3, 31 for B3

PAUSE DSMC Review

CNGA3 Study ClinicalTrials.gov Identifier: NCT02935517
CNGB3 Study ClinicalTrials.gov identifier NCT02599922

Efficacy Summary Across Both ACHMB3 and ACHMA3

ACHMB3

- Adults:
  - There are responders in visual sensitivity, light discomfort, and Quality of Life Survey; especially in the 1.1E+12 vg/ml dose, Group 5
  - In responders, the improvement in visual sensitivity was robust and durable
- Pediatrics:
  - In the 1.1E+12 vg/ml dose, Group 5, two pediatric patients had robust improvements in visual sensitivity
  - Consistent with adult data, improvements in BCVA and light discomfort may improve with time

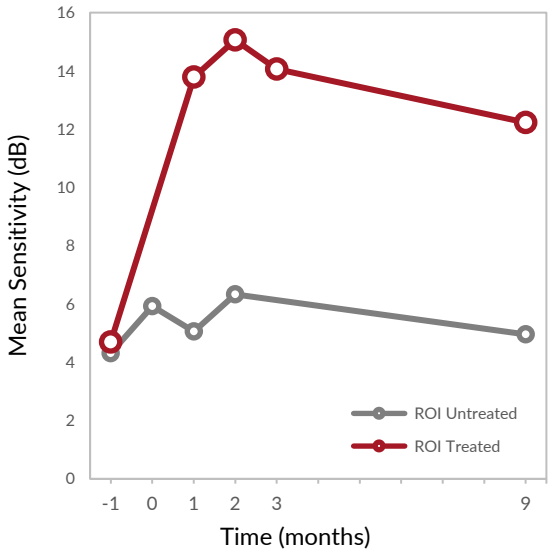
ACHMA3

- Adults and Pediatrics:
  - The majority of ACHMA3 patients have mutations that result in the production of non-functional protein
  - Results suggest that the presence of non-functional proteins may interfere with the activity of the vector expressed ACHMA3 protein
    - Data does not support advancement of clinical development

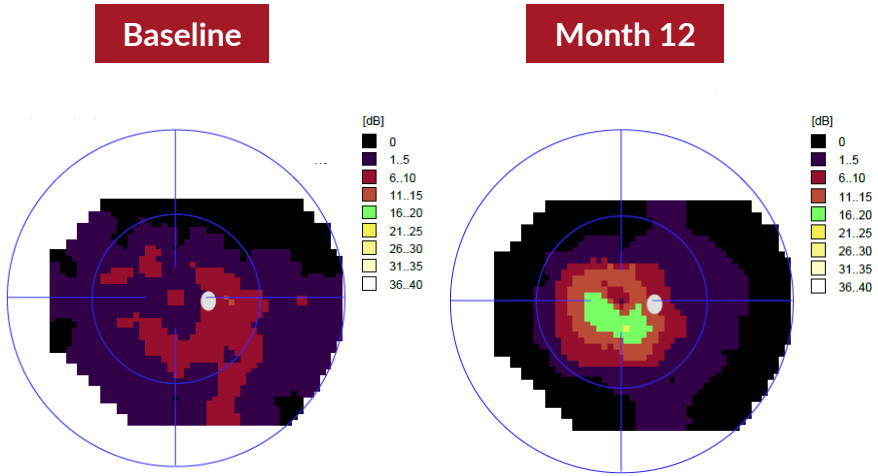
Case Study: ACHMB3 Responder Patient

Visual Sensitivity and ERG Improvements

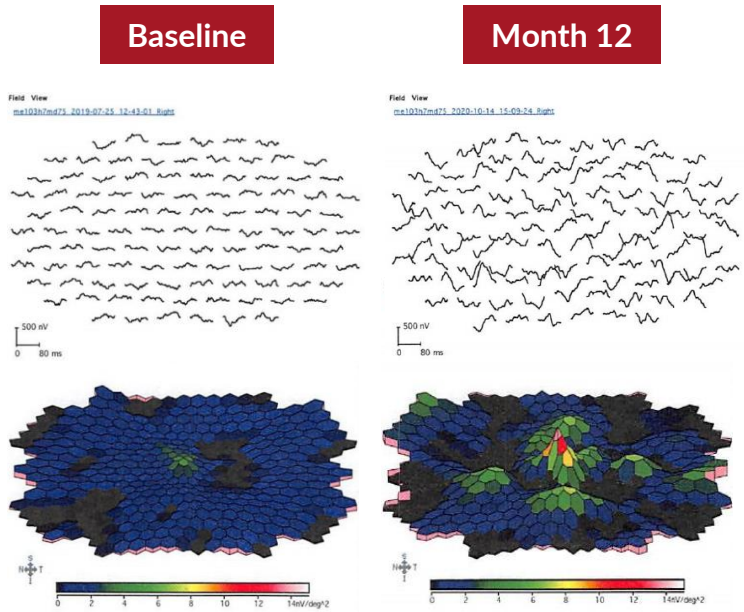
Mean Sensitivity Change (dB)
(Static Full Field Perimetry)



Sensitivity Change Heatmap (dB)
(Static Full Field Perimetry)



mfERG Change*



Age	Dose Group	Study Eye	Baseline VA	Baseline Sensitivity
53	**5**	**OD**	**OD: 43** OS: 43	**Treated: 4.7 dB** Untreated: 5.9 dB

*mfERG, or multi-focal electroretinography, a measure of electrical signaling in the retina, is not affected by patient bias

ROI = region of interest, within bleb or mirror region in untreated eye

ACHMA3 & ACHMB3

Safety Results

Non-serious Ocular Treatment Emergent Adverse Events (>20%)

regardless of causality assessment

ACHM A3	N (%)
Conjunctival hemorrhage	13 (54)
Vitreal cells	9 (38)
Conjunctival hyperemia	9 (38)
IOP increased/Ocular hypertension	8 (33)
Anterior chamber cell	8 (33)
Cataract/Cataract subcapsular	6 (25)
Eye pain	5 (21)
Subretinal fluid	5 (21)

ACHM B3	N (%)
Vitreal cells	17 (55)
Eye pain	14 (45)
Conjunctival hemorrhage	14 (45)
IOP increased/Ocular hypertension	14 (45)
Anterior chamber cell	13 (42)
Conjunctival hyperemia	10 (32)
Cataract/ Cataract subcapsular	9 (29)
Keratic precipitates	9 (29)
Subretinal fluid	7 (23)

- No systemic Treatment Emergent Adverse Events (TEAEs) >20% in either clinical study
- Most non-serious ocular TEAEs Grade 1 or 2 in severity
- All Adverse Events (AEs) due to intraocular inflammation controlled with corticosteroids

Total N=24 for A3, 31 for B3

Serious Adverse Events (SAEs)

regardless of causality assessment

ACHM A3	N (%)
Ocular	
Ocular hypertension	1 (4)
Macular hole	1 (4)
Eye inflammation*	1 (4)
Uveitis/Blindness*	1 (4)
Systematic	
Large intestine polyp	1 (4)
Radius fracture	1 (4)

ACHM B3	N (%)
Ocular	
IOP increased	1 (4)
Uveitis*	1 (4)
Systematic	
Schizoaffective disorder	1 (4)
Guillain Barre Syndrome	1 (4)
Appendicitis	1 (4)

No Dose Limiting Toxicities (DLTs) in adults

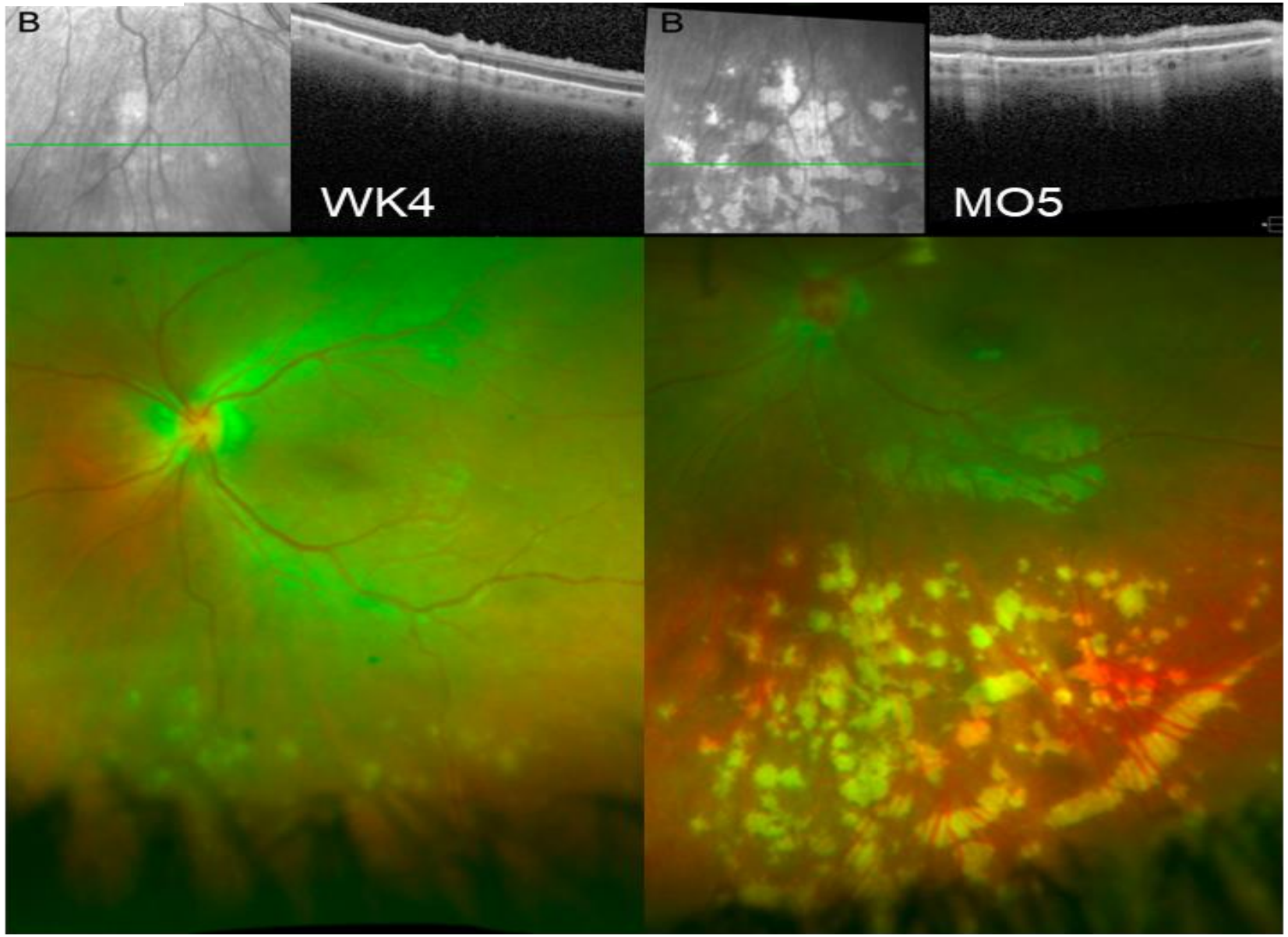
- DLT level in pediatrics deemed at highest dose ($3.2e^{12}$ vg/ml)
- *SAEs deemed Suspected Unexpected Serious Adverse Reactions (SUSARs) in 3 pediatric patients at the DLT dose level
- SUSARs responded to an adjusted corticosteroid regimen
- SAE of uveitis/blindness study eye had SRF reported fellow eye

Below the highest dose level ($3.2e^{12}$ vg/ml)

- No drug-related SAEs
- Similar safety profiles observed in pediatric and adult patients

Total N=24 for A3, 31 for B3

Case Study



Safety Conclusions

- The highest dose studied ($3.2e^{12}$vg/mL) was assessed to be a DLT level in pediatric subjects based on intraocular inflammation that responded to an adjusted steroid regimen
- AGTC-401/AGTC-402 gene therapy to potentially treat ACHM was safe and well-tolerated in adults up to and including the highest dose ($3.2e^{12}$vg/mL), and in children up to and including second highest dose ($1.1e^{12}$ vg/mL). Both drugs had a favorable safety profile at dose levels below the DLT
- Insights gained to be incorporated into Phase 3 clinical development of AGTC-401 (CNGB3)

Thank you

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