Findings on visual photosensitivity in two phase 1/2 clinical trials of subretinal gene therapy with AGTC-401 and AGTC-402 for *CNGB3* and *CNGA3* achromatopsia

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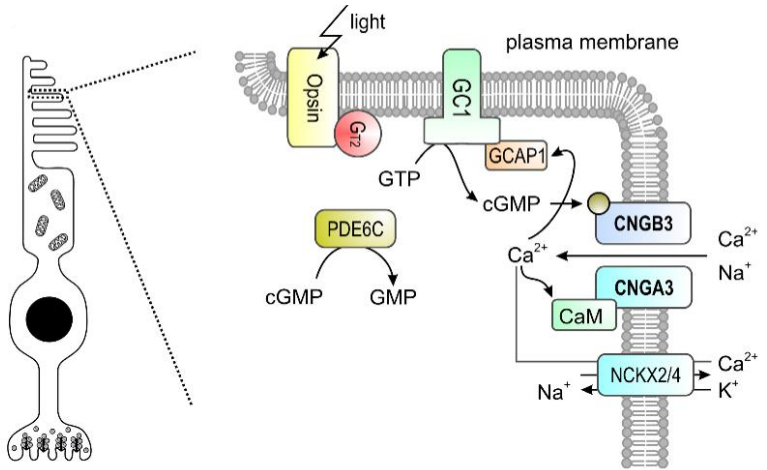
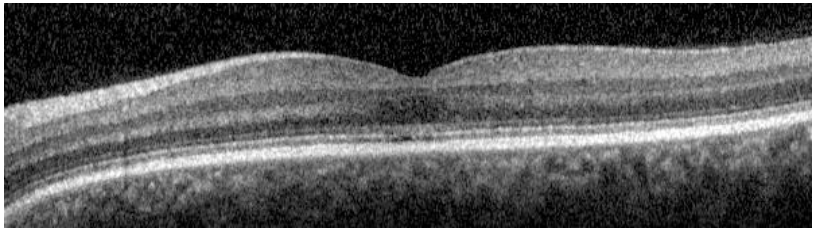
Achromatopsia (ACHM)

- Congenital cone dysfunction
- Clinical manifestations: Decreased visual acuity, photosensitivity, absent color discrimination
- The genes *CNGA3* and *CNGB3* account for 25% and 50% of ACHM
- Residual cone structure provides therapeutic target
- Animal models support benefit of gene therapy





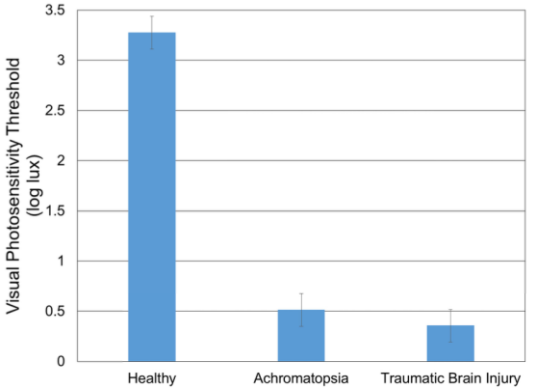
Structure-function dissociation in OCT from achromatopsia patient

Methods

- Phase 1/2 open-label dose escalation trials
  - CNGA3: NCT02935517
  - CNGB3: NCT02599922
- Eligibility criteria included:
  - Biallelic *CNGA3* or *CNGB3* mutations
  - Best-corrected visual acuity difference ≤15 ETDRS letters
- Study drugs
  - AGTC-402 (rAAV2tYF-PR1.7-hCNGA3)
  - AGTC-401 (rAAV2tYF-PR1.7-hCNGB3)
- Delivery: Subretinal injection with typical volume of 300 µL
- Primary outcome: Safety
  - ***Poster A0345 on May 3, Dr. Alessandro Iannaccone***
- Secondary outcomes include:
  - Visual acuity
  - **Photosensitivity**
  - Visual field sensitivity
    - Results presented at RD2021 meeting
  - Perceived color brightness
  - Retinal structure
  - Patient-reported outcomes

Photosensitivity: Relevance and assessment

- Impact of photosensitivity in survey of ACHM patients:
  - 96% of respondents: Limits ability to conduct daily activities
  - 73%: Limits job opportunities
  - 38%: Photosensitivity is the aspect of their vision that they would choose to improve
- Two tests to assess:
  - LDT-1: Light of increasing intensity presented using an adapted Ganzfeld dome
  - LDT-2: Ocular photosensitivity analyzer (OPA)
  - In both, stimuli of increasing intensity are presented until participant indicates discomfort
  - **A change of 1 log lux is statistically and clinically relevant**



Aboshiha IOVS 2017: 58(9), 3537–3546; Aguilar Biomed Opt Express 2018:9(11), 5583-96

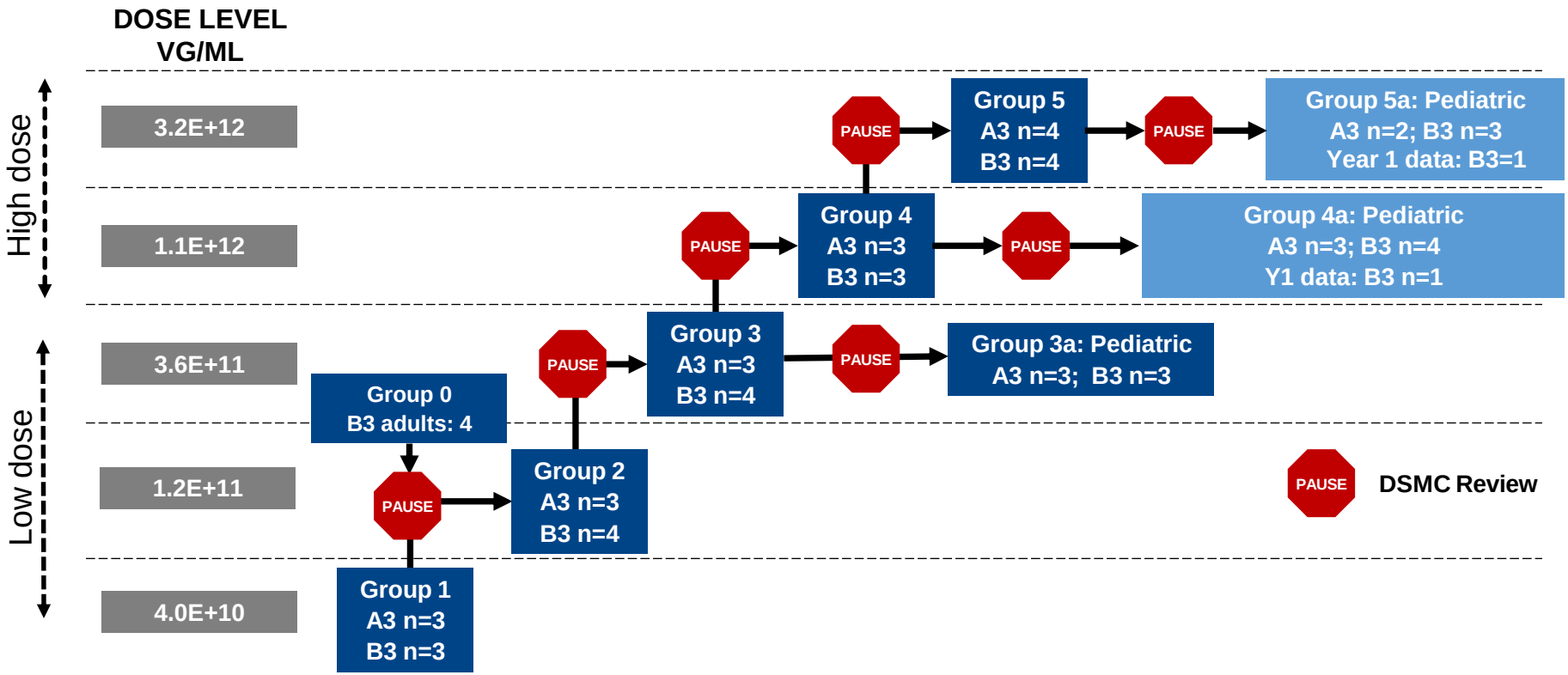
1 log lux in real-world terms

Lux level estimate	Interpretation comparison
1	Twilight
5	Minimal street lighting
10	Sunset
50	Family living room
80	Hallway
100	Very dark overcast day
320–500	Office lighting
400	Sunrise/sunset
1000	Overcast day
10,000–25,000	Full daylight
32,000–130,000	Direct sunlight

Source: Hawks (2012).

Health Psychol Open. 2016 Jan; 3(1): 2055102916648679.

Dose escalation



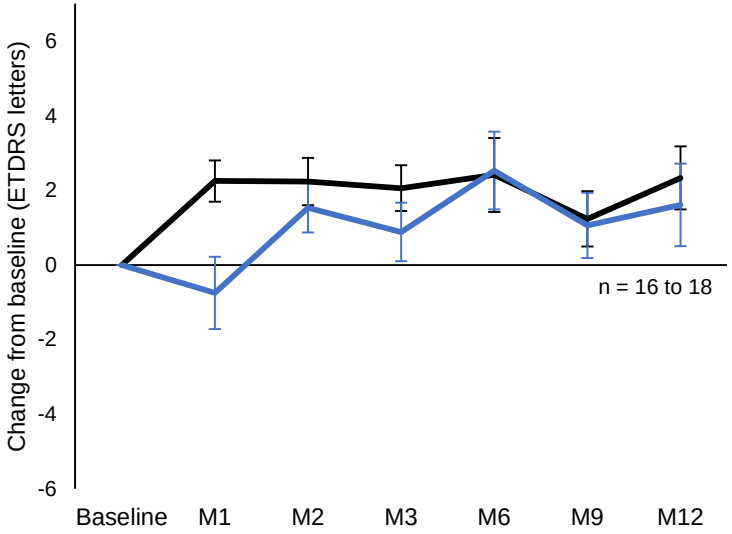
Baseline characteristics

	CNGA3 (n=24)	CNGB3 (n=31)
Female	9 (38%)	16 (52%)
Adult participants	16 (67%)	21 (68%)
Pediatric participants	8 (33%)	10 (32%)
Baseline visual function, study eye; Mean (standard deviation)		
BCVA (ETDRS)	41.4 (5.9)	40.0 (8.4)
Retinal sensitivity (dB)*	4.9 (3.4)	5.3 (5.2)
Light discomfort threshold (log lux)	1.1 (0.8)	0.9 (0.7)

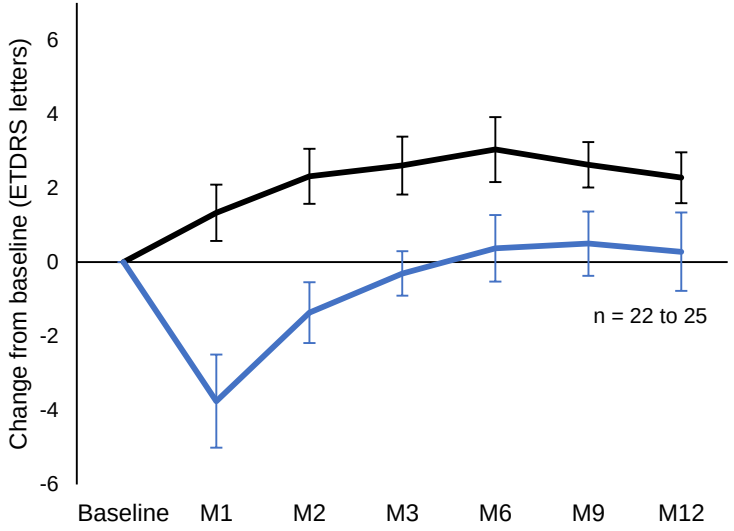
*Mean sensitivity within bleb-treated area measured with Octopus full field static perimetry (red stimulus)

Visual acuity is maintained

CNGA3: Mean change from baseline



CNGB3: Mean change from baseline



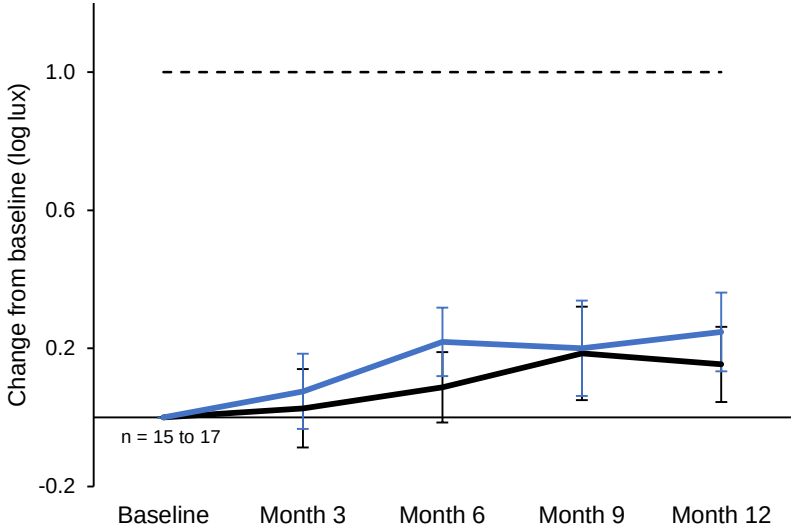
Error bars: Standard error

Study eye

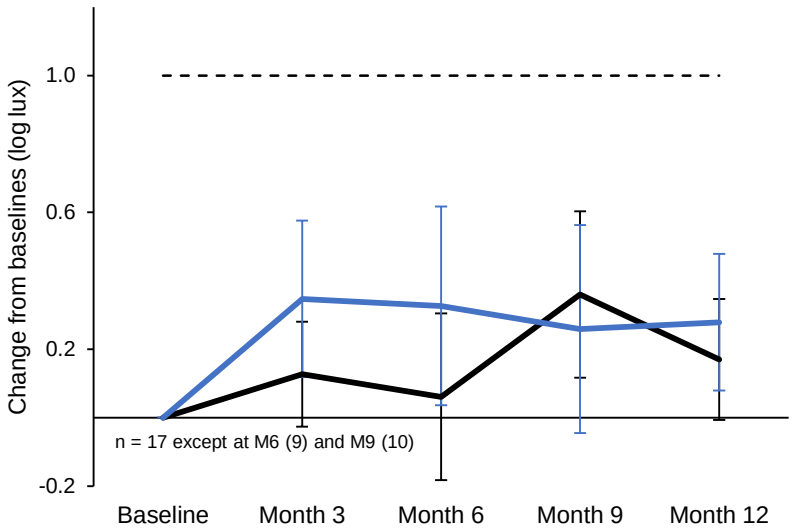
Fellow eye

CNGA3: Mean photosensitivity is stable

LDT-1: Mean change from baseline



LDT-2: Mean change from baseline



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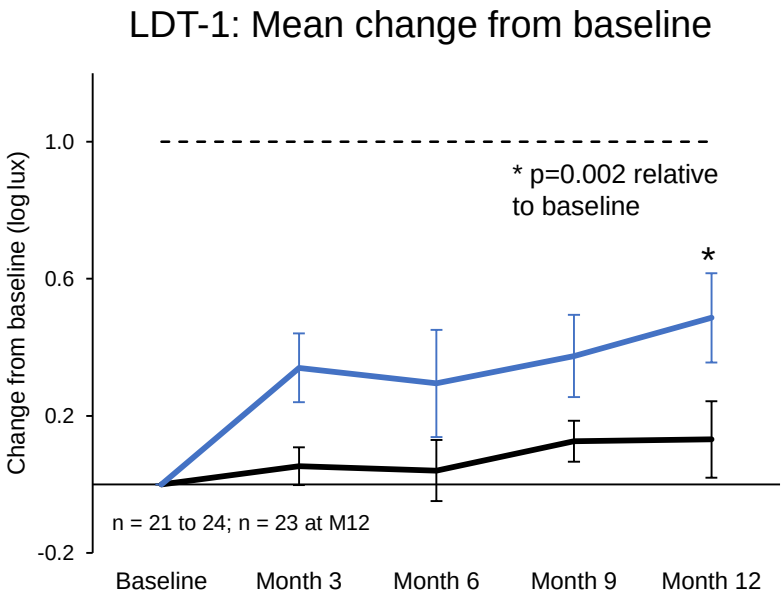
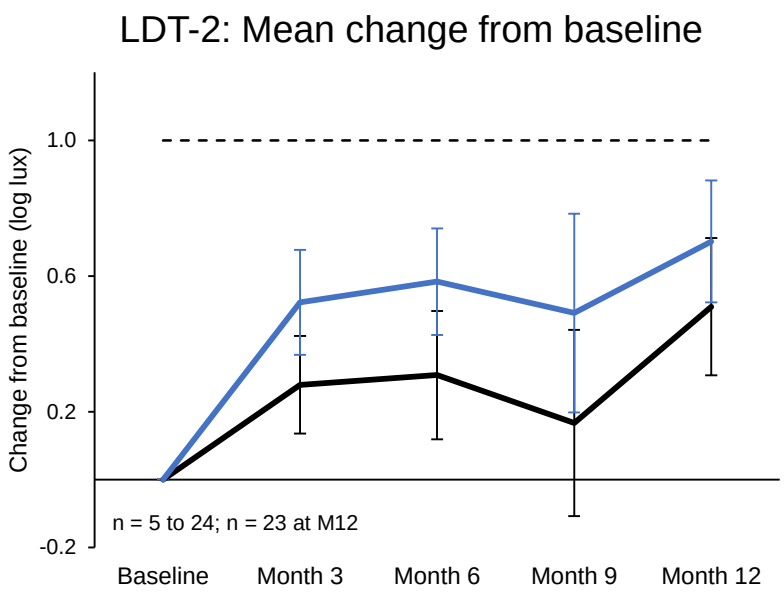
Study eye Fellow eye

CNGB3: Mean photosensitivity is improved





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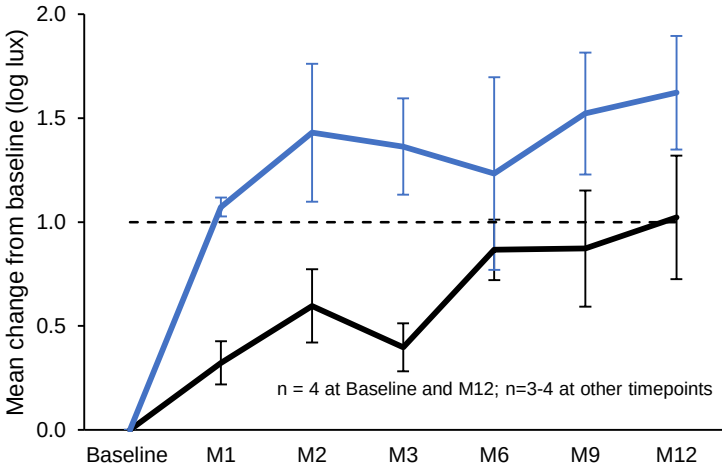
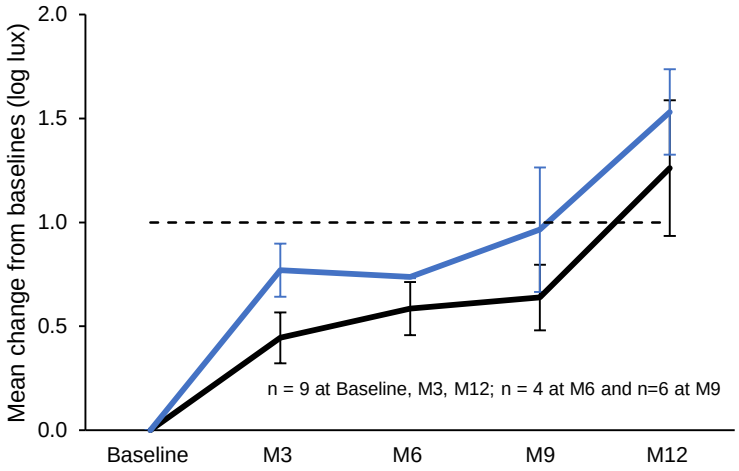
Study eye Fellow eye

CNGB3: Responder analysis

LDT-1 responders (n = 4)



LDT-2 responders (n = 9)



- All LDT-1 responders are also LDT-2 responders
- Month 24 data available for 2 individuals and shows sustained improvement on both tests

Error bars: Standard error

Study eye Fellow eye

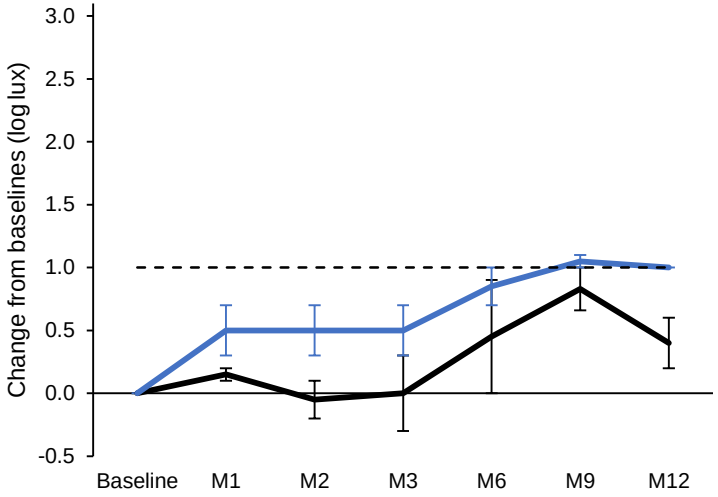
CNGB3: Summary of responders

Group (LDT-1 n; LDT-2 n)	LDT-1		LDT-2	
	Study eye	Fellow eye	Study eye	Fellow eye
Overall (n = 23; n = 23)	17% (n = 4)	13% (n=3)	39% (n=9)	30% (n=7)
Low dose (n = 13; n = 14)	8% (n=1)	8% (n=1)	29% (n=4)	29% (n=4)
High dose (n = 10; n = 9)	30% (n=3)	20% (n=2)	56% (n=5)	33% (n=3)
Pediatric (n = 3; n = 2)	0%	0%	50% (n=1)	50% (n=1)

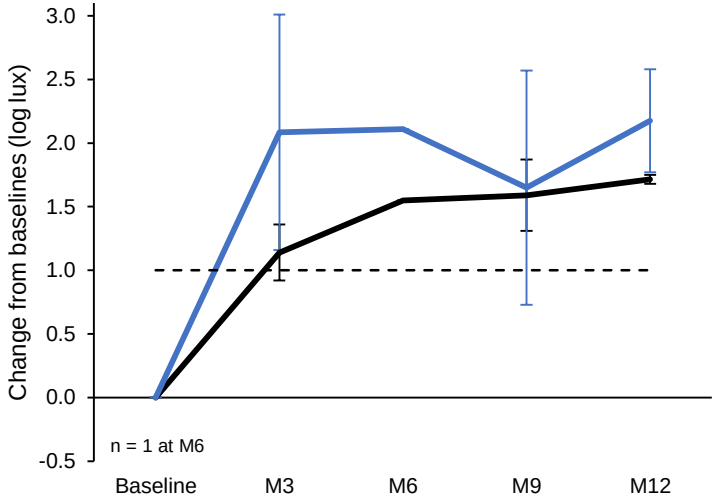
* Includes pediatric participants

CNGA3: Responder analysis

LDT-1 responders (n = 2)



LDT-2 responders (n = 2)



- Three participants show improved photosensitivity
- Month 24: All improvement is sustained

Error bars: Standard error

Study eye Fellow eye

Summary

- CNGB3: Subretinal gene therapy with AGTC-401 improved photosensitivity in some participants
- CNGA3: Improved photosensitivity after treatment with AGTC-402 occurred less frequently
- Improvements in photosensitivity are sustained at Month 24 for patients with available data
- Questions raised by data:
  - Are there patient-level characteristics that predict improvement?
  - Are there correlates between improvement in photosensitivity and other outcomes?
  - Why are responses bilateral?

Acknowledgements

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