

FALCON Natural History Study: Longitudinal Assessment of Functional and Anatomical Changes in *OPA1* Autosomal Dominant Optic Atrophy

Patrick Yu-Wai-Man¹⁻³, Piero Barboni⁴, Marc Bouffard⁵, Julie Falardeau⁶, Chiara La Morgia⁷, Byron Lam⁸, Michael Larsen⁹, Raghu Mudumbai¹⁰, Marcela Votruba¹¹, Barry Ticho¹², Steven Gross¹², Alice Wyse Jackson¹², Kelly Saluti¹², Yue Wang¹², James Stutely¹², Yaping Joyce Liao¹³

¹Cambridge Eye Unit, Addenbrooke's Hospital, Cambridge University Hospitals, Cambridge, United Kingdom; ²Moorfields Eye Hospital NHS Foundation Trust, London, United Kingdom; ³Institute of Ophthalmology, University College London, London, United Kingdom; ⁴IRCCS San Raffaele Scientific Institute, Milan, Italy; ⁵Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, Massachusetts, United States; ⁶Casey Eye Institute, Oregon Health & Science University, Portland, Oregon, United States; ⁷Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy; ⁸Miller School of Medicine, University of Miami, Miami, Florida, United States; ⁹Rigshospitalet Glostrup, University of Copenhagen, Copenhagen, Denmark; ¹⁰Department of Ophthalmology, University of Washington, Seattle, Washington, United States; ¹¹School of Optometry & Vision Sciences, University of Cardiff, Cardiff, United Kingdom; ¹²Stoke Therapeutics, Bedford, Massachusetts, United States; ¹³Byers Eye Institute, Stanford University, Palo Alto, California, United States.

Financial Disclosures

Patrick Yu-Wai-Man	GenSight Biologics, Chiesi Farmaceutici, Stoke Therapeutics, PYC Therapeutics – C GenSight Biologics, Santhera Pharmaceuticals – I
Piero Barboni	Omikron, GenSight Biologics, Chiesi Farmaceutici – X
Marc Bouffard	None
Julie Falardeau	Stoke Therapeutics – G
Chiara La Morgia	Chiesi Farmaceutici, GenSight Biologics, Regulatory Pharma Net, Thenewway – C Santhera Pharmaceuticals, Chiesi Farmaceutici, GenSight Biologics, Regulatory Pharma Net, Thenewway, First Class, Biologix – I GenSight Biologics, Santhera Pharmaceuticals, Stoke Therapeutics, Reneo Pharmaceuticals, OMEICOS – G
Byron Lam	National Eye Institute, United States Department of Defense, Foundation Fighting Blindness, Atsena Therapeutics, Beacon Therapeutics, Endogena Therapeutics, Nanoscope Therapeutics, Ocugen, PYC Therapeutics, SparingVision, Spark Therapeutics, SpliceBio, Stoke Therapeutics – H BlueRock Therapeutics, Johnson & Johnson, SpliceBio, Spulbio – C
Michael Larsen	Stoke Therapeutics – C, G Novo Nordisk, Bayer, Roche, Janssen Pharmaceuticals (now Johnson & Johnson Innovative Medicine), Novartis – C
Raghu Mudumbai	Stoke Therapeutics, Viridian Therapeutics, Nicox – G
Marcela Votruba	Fight for Sight – H, Transine Therapeutics, Chiesi Farmaceutici, Stoke Therapeutics – C Stoke Therapeutics, Chiesi Farmaceutici – I
Barry Ticho	Stoke Therapeutics – F
Steven Gross	Stoke Therapeutics – F
Alice Wyse Jackson	Stoke Therapeutics – F
Kelly Saluti	Stoke Therapeutics – F
Yue Wang	Stoke Therapeutics – F
James Stutely	Stoke Therapeutics – F
Yaping Joyce Liao	Stoke Therapeutics – C

Introduction

ADOA is an inherited progressive optic neuropathy primarily caused by mutations in the *OPA1* gene



1 in **35,000** people
are affected globally^{*,1}



80% of patients are
symptomatic by age 10¹

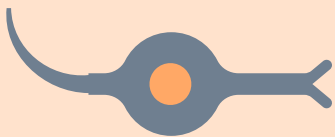


Up to **46%** of patients are
registered as legally blind¹

65%–90%
of cases are caused by
mutations in the *OPA1* gene²



50%
OPA1 protein expression and
disease manifestation



OPA1 protein is critical for mitochondrial health in retinal ganglion cells; its loss disrupts energy production and results in cell death, leading to vision impairment³

FALCON was a multicenter, 24-month, natural history study of 47 patients with ADOA

FALCON aimed to provide a better understanding of how ADOA disease parameters **change over time** to inform potential future interventional clinical trials

^{*}Incidence in Denmark estimated to be closer to 1 in 10,000 because of founder effect.

ADOA, autosomal dominant optic atrophy; OPA1, OPA1 mitochondrial dynamin like GTPase.

1. Yu-Wai-Man P et al. *Ophthalmology* 2010; 117 (8): 1538–1546. 2. Chun BY et al. *Curr Opin Ophthalmol* 2016; 27 (6): 475–480. 3. Lenaers G et al. *Int J Biochem Cell Biol* 2009; 41 (10): 1866–1874.

FALCON natural history study

Eligibility criteria

- ✓ Clinical diagnosis of ADOA with confirmed heterozygous *OPA1* variant; ≥ 5 ETDRS letter score
- ✗ GOF variant; compound heterozygous or homozygous pathogenic / likely pathogenic variant; benign / likely benign variant (*OPA1* or other); phenotypic manifestation of syndromic ADOA

Primary endpoints

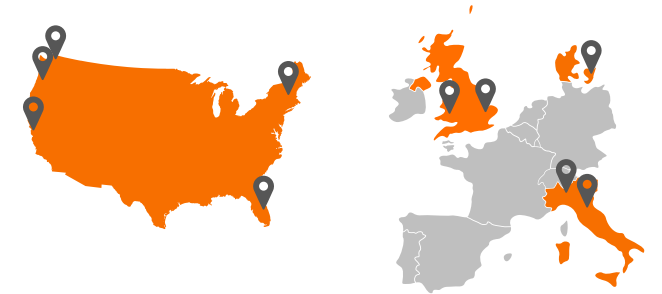
- Change from baseline to Month 24 in BCVA (ETDRS); visual field sensitivity (Humphrey 10-2 automated perimetry); pRNFL thickness (OCT); macular GCL/IPL thickness (OCT)

Exploratory

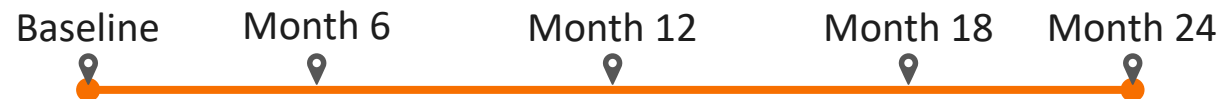
- *In vivo* imaging of retinal mitochondria using OcuMet Beacon™ (OcuSciences Inc.)

10 study sites

- USA (5)
- Italy (2)
- UK (2)
- Denmark (1)



Assessment timeline



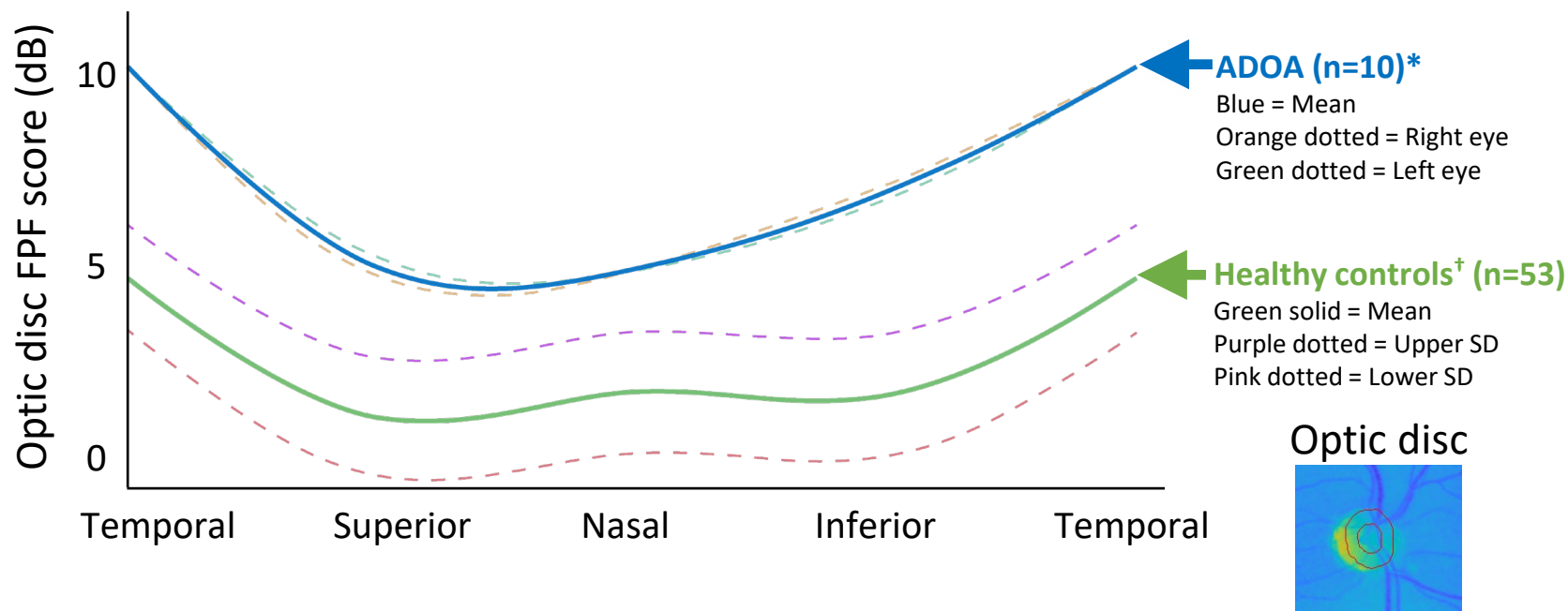
FALCON baseline demographics

Baseline demographics	8–17 years (n=15)	18–40 years (n=21)	41–60 years (n=11)	Total (N=47)
Mean age at screening in years (SD)	13.0 (2.9)	28.2 (6.2)	48.3 (6.0)	28.1 (14.1)
Female, n (%)	8 (53%)	7 (33%)	6 (54%)	21 (47%)
Mean logMAR	0.53	0.45	0.85	0.57
Mean pRNFL global thickness	70.6*	64.9	56.4	64.5 [†]

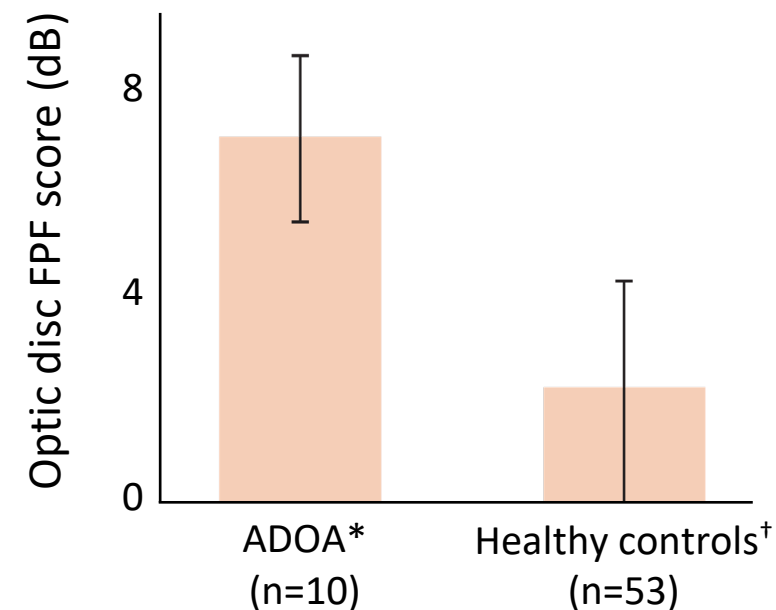
*n=13. [†]N=45.
logMAR, logarithm of the minimum angle of resolution; pRNFL, peripapillary retinal nerve fiber layer; SD, standard deviation.

At baseline, mitochondrial stress as measured using optic disc FPF scores is higher in patients with ADOA

Optic disc FPF scores for patients 30–60 years of age

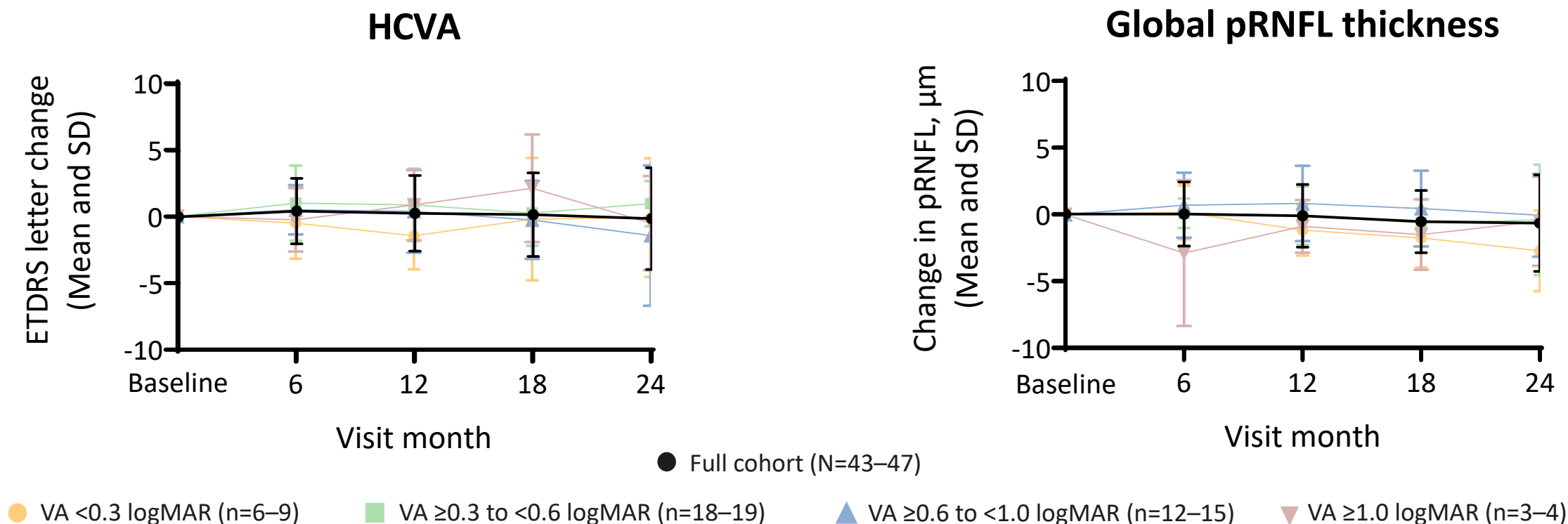


Baseline optic disc FPF global scores



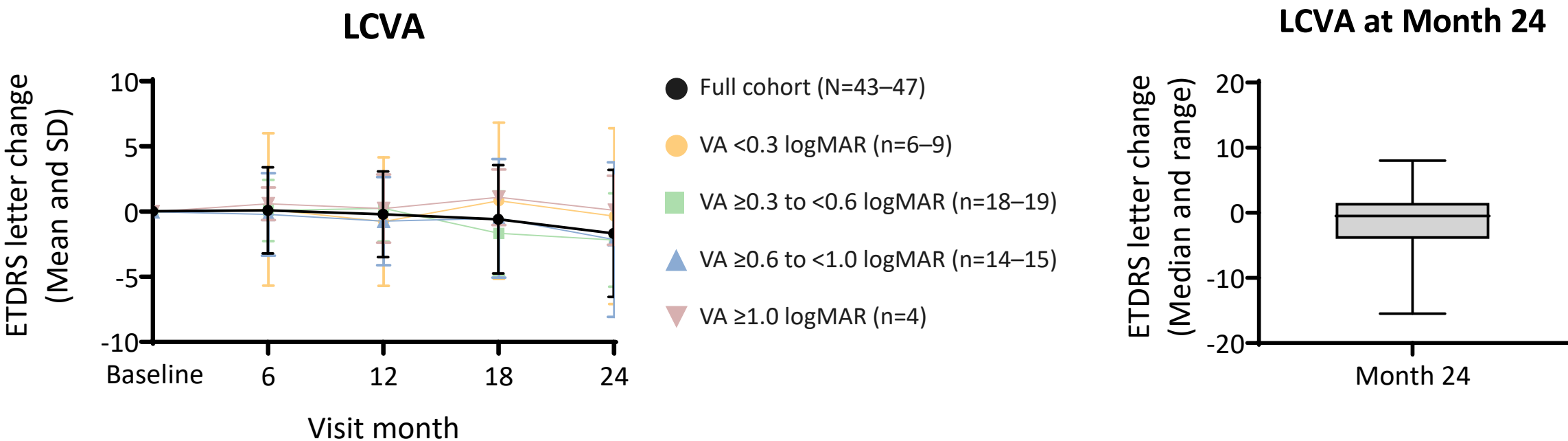
FPF scores are higher across all sectors in ADOA patients compared with healthy controls

Minimal change in HCVA and pRNFL thickness was observed in ADOA over 24 months



Although pRNFL loss is a feature of ADOA, no detectable change in mean HCVA or pRNFL thickness is observable over a short time frame

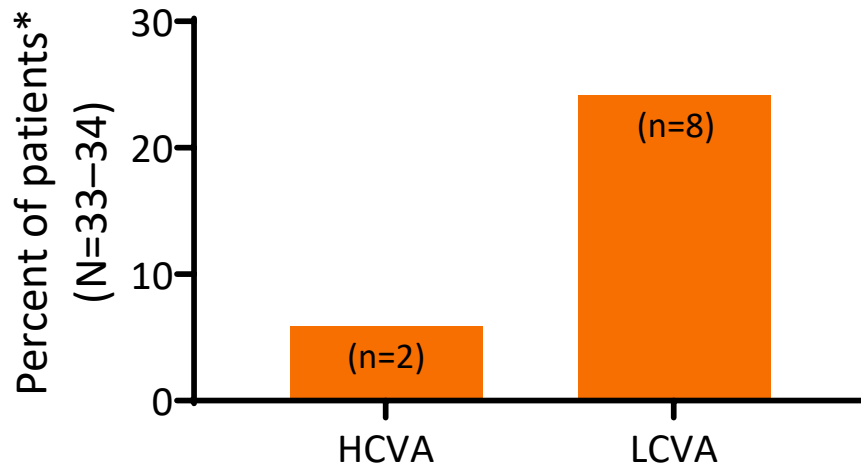
Modest decline in LCVA was observed in ADOA over 24 months



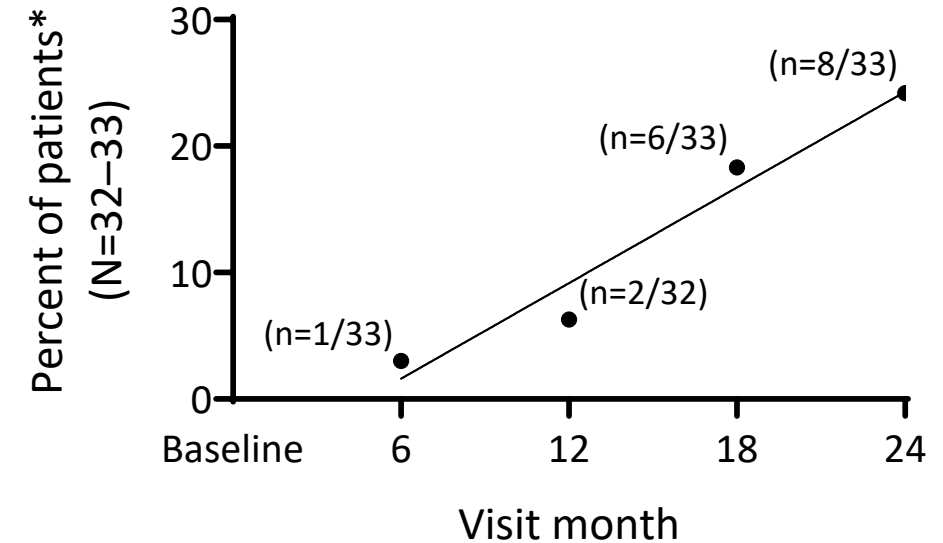
While overall change was modest, individual LCVA trajectories showed cases of significant decline over 24 months

Proportion of patients with ≥ 5 ETDRS letter loss in LCVA increases over time

Patients with ≥ 5 ETDRS letter loss at Month 24



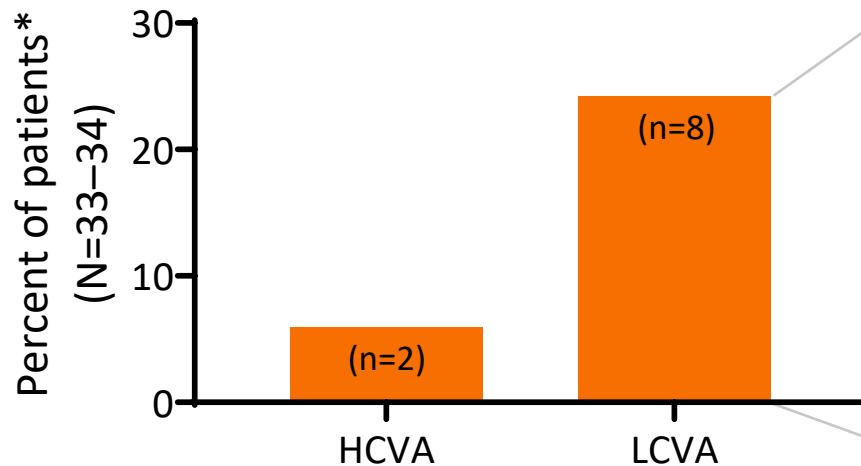
Patients with ≥ 5 ETDRS letter loss in LCVA over 24 months



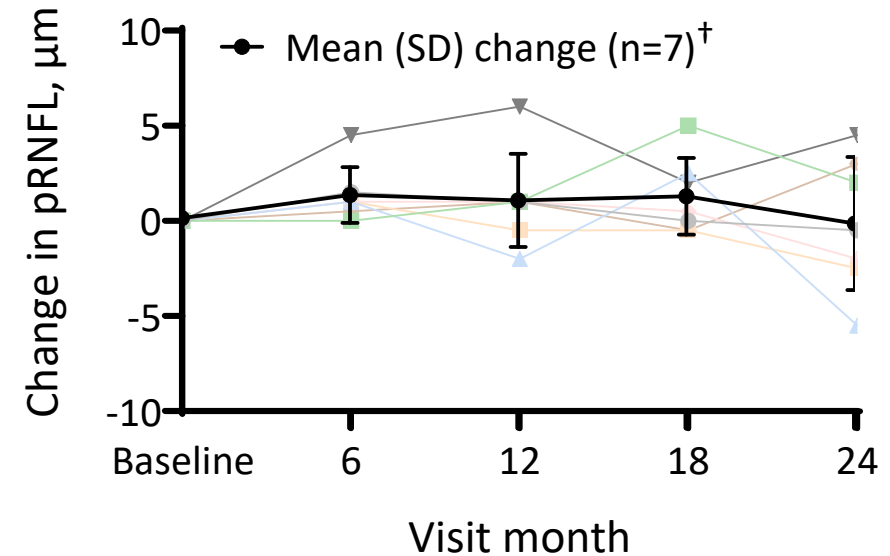
LCVA may serve as a sensitive measure of ADOA disease progression

No change in pRNFL detected in patients with >5 ETDRS letter loss

Patients with ≥ 5 ETDRS letter loss at Month 24



pRNFL thickness in individual patients with ≥ 5 ETDRS letter loss in LCVA



Stable pRNFL thickness over 24 months and mitochondrial stress suggest LCVA changes may be functionally driven at the cellular level and potentially reversible

Month 24 data cut: July 11, 2025. *Percent of patients with baseline VA ≥ 0.3 to < 1.0 logMAR. [†]One patient did not complete the baseline pRNFL assessment and was excluded from the pRNFL analysis.

ETDRS, Early Treatment Diabetic Retinopathy Study; HCVA, high-contrast visual acuity; LCVA, low-contrast visual acuity; logMAR, logarithm of the minimum angle of resolution; pRNFL, peripapillary retinal nerve fiber layer; RNFL, retinal nerve fiber layer; SD, standard deviation; VA, visual acuity

Conclusions

- 1 FALCON data confirm that while *OPA1*-associated ADOA progresses slowly, it causes profound deficits in visual function that worsen with age
- 2 Patients with ADOA have greater mitochondrial stress compared with healthy controls as measured by FPF
- 3 LCVA may serve as a sensitive measure of disease progression in ADOA
- 4 Stable anatomy over 24 months suggests that short-term decline in LCVA may be caused by cellular deficits that could be reversible
- 5 LCVA and FPF may provide measurable parameters to assess potential treatment efficacy in ADOA

References

1. Yu-Wai-Man P *et al. Ophthalmology* 2010; 117 (8): 1538–1546.
2. Chun BY *et al. Curr Opin Ophthalmol* 2016; 27 (6): 475–480.
3. Lenaers G *et al. Int J Biochem Cell Biol* 2009; 41 (10): 1866–1874

Thank you

This study was supported by Stoke Therapeutics.

**We thank investigators, health care providers,
site staff, and patients who participated in the study.**