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FALCON Natural History Study: Identifying Sensitive Measures of Change in *OPA1*-Associated ADOA

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Disclosures

- Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Chiesi Pharma
- Payment for expert testimony from Omikron Farma
- Data Safety Monitoring Board or Advisory Board member for Soke Pharma, Chiesi Pharma, Omikron Farma, and Gensight

Autosomal dominant optic atrophy is a progressive optic neuropathy[1,2]

Prevalence[1]

1 in **35,000** people are affected

Pathophysiology[2,3]

ADOA is primarily caused by ***OPA1* gene variants** that reduce OPA1 protein expression, resulting in **mitochondrial dysfunction**, **retinal ganglion cell loss**, and **progressive visual impairment**

Treatments[4]

There are currently **no approved treatments** for ADOA

FALCON was a prospective natural history study that evaluated structural and functional changes in the retina and optic nerve of patients with *OPA1* ADOA over 24 months

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

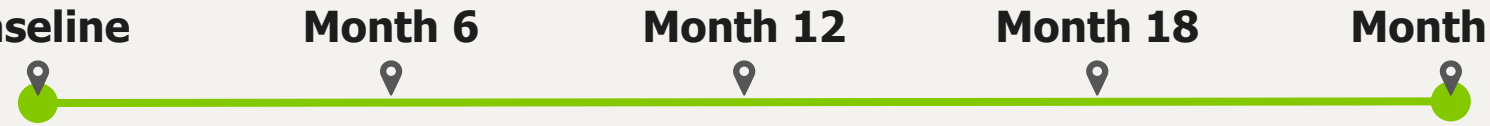
1. Yu-Wai-Man P *et al. Ophthalmology* 2010; 117 (8): 1538–1546. 2. Chun BY *et al. Curr Opin Ophthalmol* 2016; 27 (6): 475–480. 3. Lenaers G *et al. Prog Retin Eye Res* 2021; 83: 100935. 4. Autosomal Dominant Optic Atrophy Association. So…What is ADOA? Available at: https://www.adoaa.org/what-is-adoa. Accessed May 2026.

FALCON study design

FALCON enrolled 48 patients across 10 study sites,
with assessments at baseline and Months 6, 12, 18, and 24

Eligibility criteria

- Age ≥8 to ≤60 years
- Clinical diagnosis of ADOA and heterozygous *OPA1* gene variant
- ≥5 ETDRS letter score
- GOF variants and phenotypic manifestations of syndromic ADOA were excluded



Study endpoints

Change from baseline to Month 24 in pRNFL thickness, HCVA, and LCVA

HCVA and LCVA were assessed using ETDRS optotypes, while pRNFL thickness was assessed using optical coherence tomography.
ADOA, autosomal dominant optic atrophy; ETDRS, Early Treatment Diabetic Retinopathy Study; GOF, gain-of-function; HCVA, high-contrast visual acuity; LCVA, low-contrast visual acuity; *OPA1*, OPA1 mitochondrial dynamin like GTPase; pRNFL, peripapillary retinal nerve fiber layer.

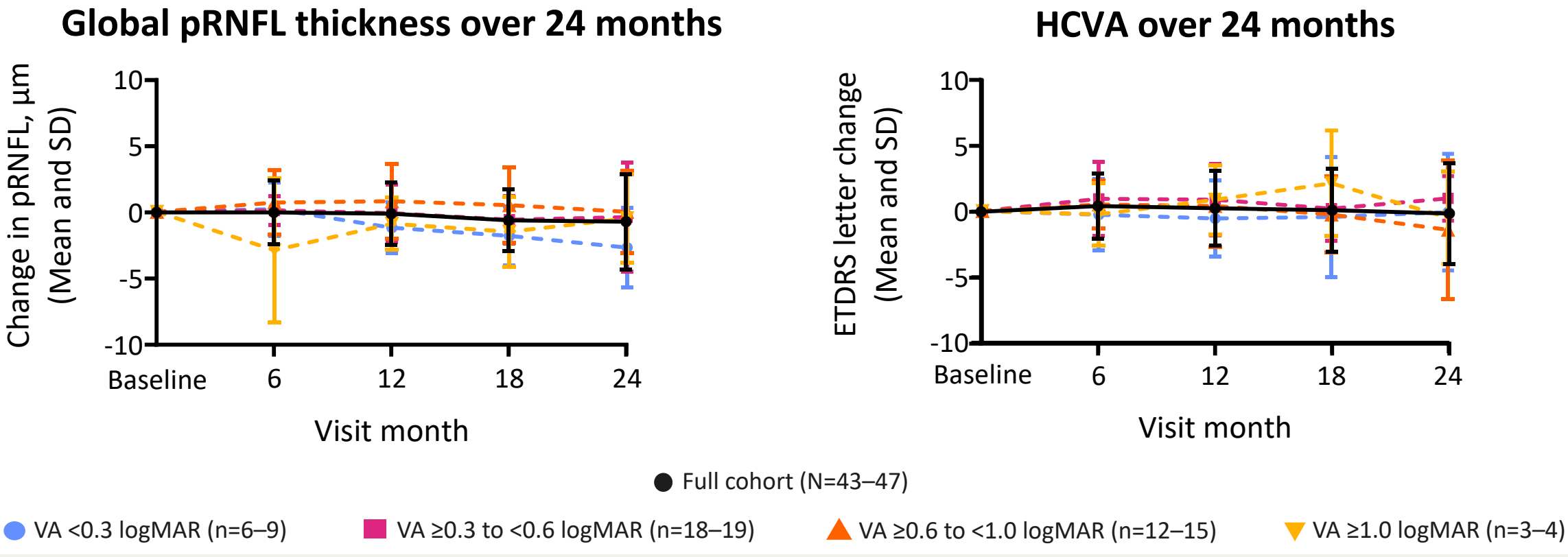
FALCON baseline demographics

Of the 48 patients enrolled, 47 were analyzed

Baseline demographics	8–17 years (n=15)	18–40 years (n=21)	41–60 years (n=11)	Total (N=47)
Mean age in years (SD)	13.0 (2.90)	28.2 (6.16)	48.3 (5.97)	**28.1** (14.09)
Female, n (%)	8 (53.3%)	7 (33.3%)	6 (54.5%)	21 (44.7%)
Mean logMAR (SD)	0.5 (0.25)	0.4 (0.25)	0.9 (0.44)	**0.6** (0.34)
Mean pRNFL global thickness in µm (SD)	70.6 (12.53)[a]	64.9 (13.46)	56.4 (9.18)	64.5 (13.12)[b]

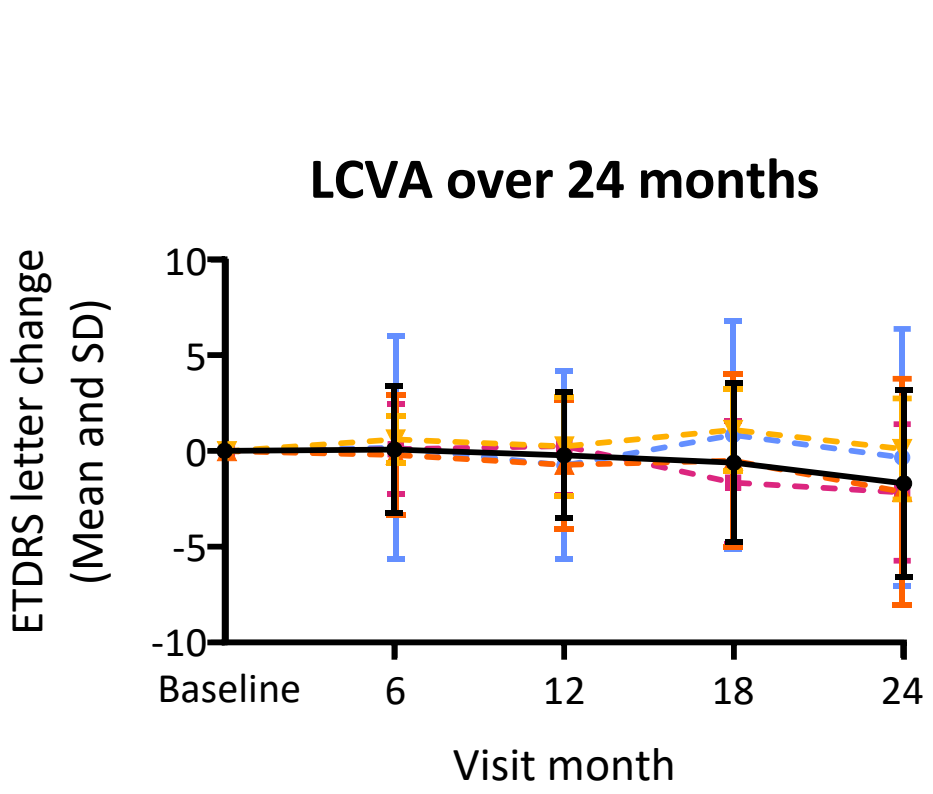
[a]n=13. [b]N=45.
logMAR, logarithm of the minimum angle of resolution; pRNFL, peripapillary retinal nerve fiber layer; SD, standard deviation.

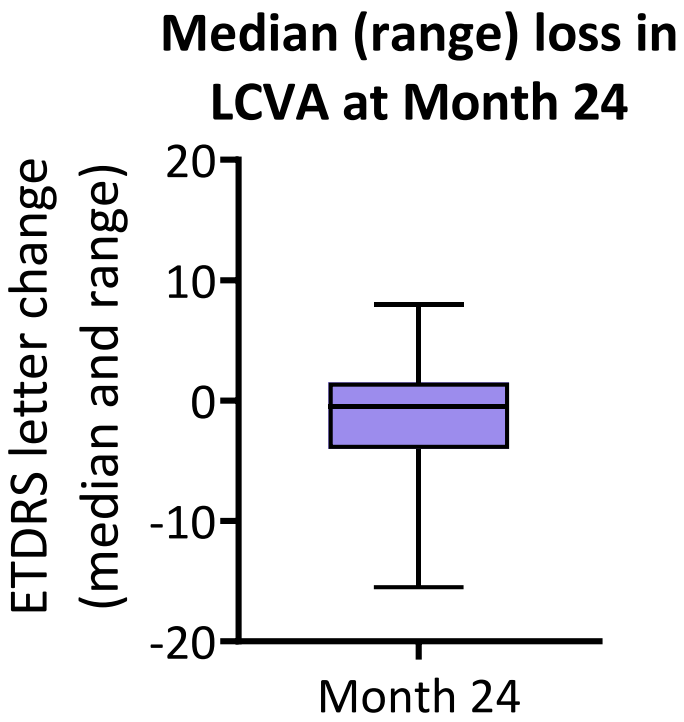
Minimal changes in retinal anatomy and HCVA were observed over 24 months



Month 24 data cut: July 11, 2025.
ETDRS, Early Treatment Diabetic Retinopathy Study; HCVA, high-contrast visual acuity; logMAR, logarithm of the minimum angle of resolution; pRNFL, peripapillary retinal nerve fiber layer; SD, standard deviation; VA, visual acuity.

Modest declines in LCVA were observed over 24 months



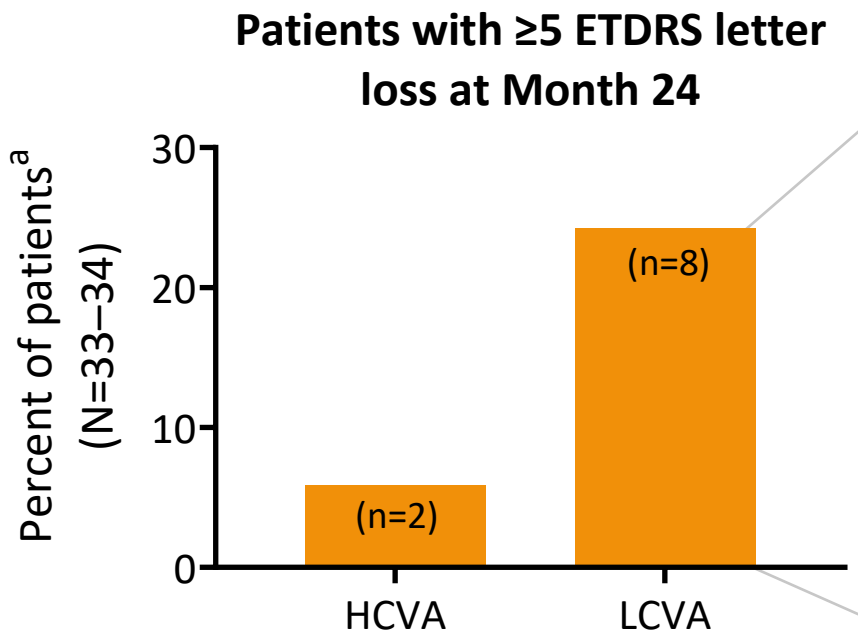


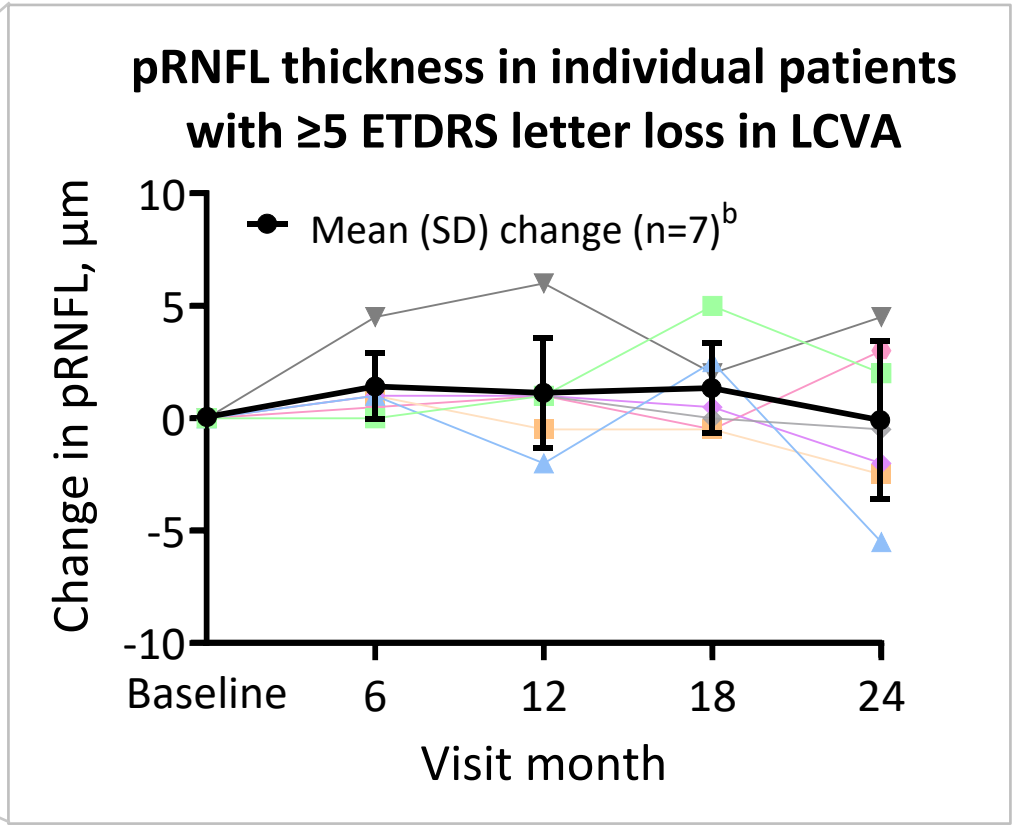
● Full cohort (N=43–47)

● VA <0.3 logMAR (n=6–9) ■ VA ≥0.3 to <0.6 logMAR (n=18–19) ▲ VA ≥0.6 to <1.0 logMAR (n=12–15) ▼ VA ≥1.0 logMAR (n=3–4)

Month 24 data cut: July 11, 2025.
ETDRS, Early Treatment Diabetic Retinopathy Study; LCVA, low-contrast visual acuity; logMAR, logarithm of the minimum angle of resolution; SD, standard deviation; VA, visual acuity.

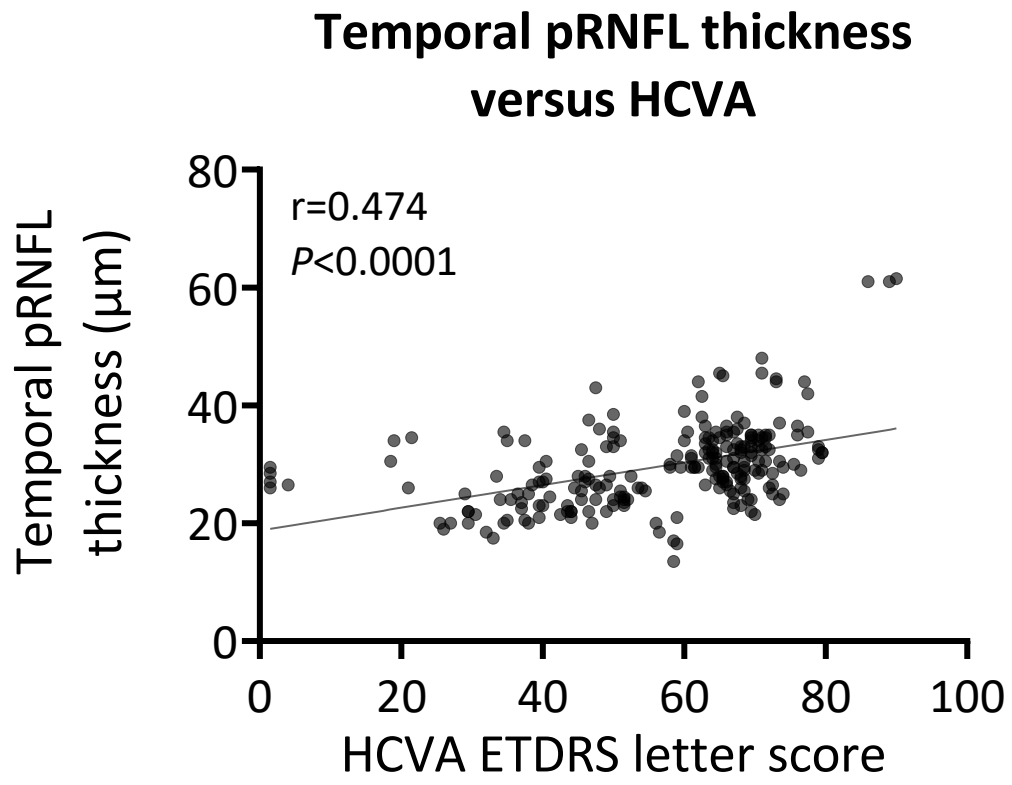
LCVA decline over 24 months was observed despite no change in pRNFL thickness

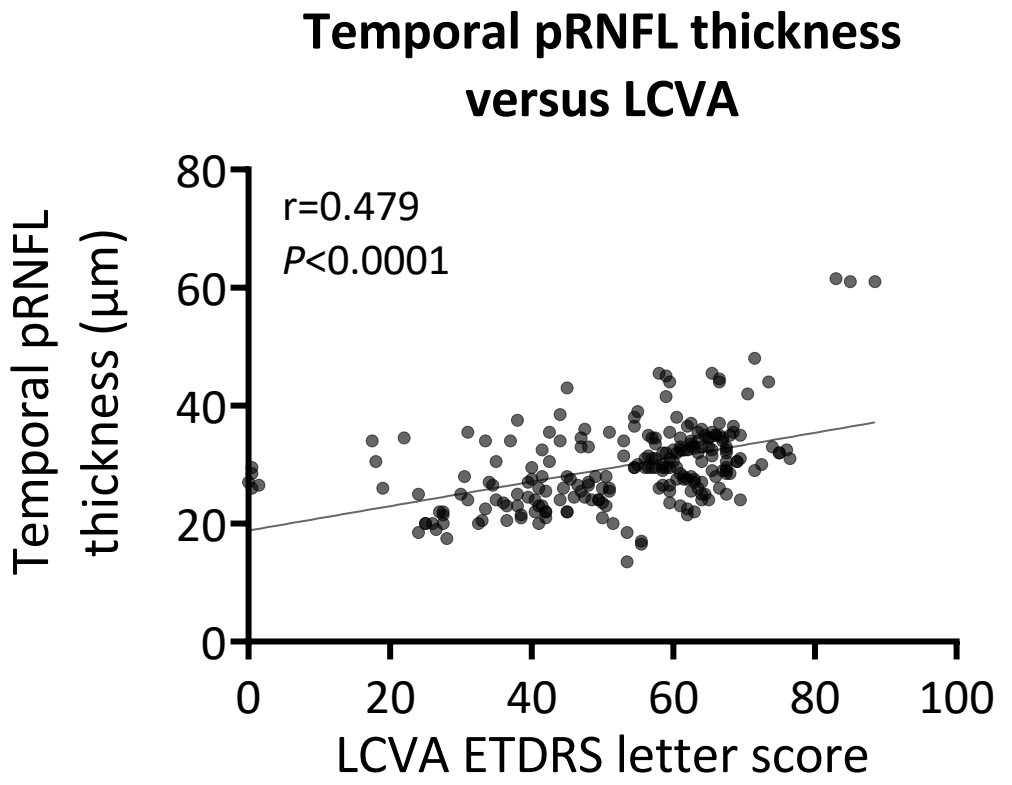




Month 24 data cut: July 11, 2025.
[a]Subgroup of patients with baseline visual acuity ≥0.3 to <1.0 logMAR. [b]One patient did not complete the baseline pRNFL assessment and was excluded from the pRNFL analysis.
ETDRS, Early Treatment Diabetic Retinopathy Study; HCVA, high-contrast visual acuity; LCVA, low-contrast visual acuity; logMAR, logarithm of the minimum angle of resolution; pRNFL, peripapillary retinal nerve fiber layer; SD, standard deviation.

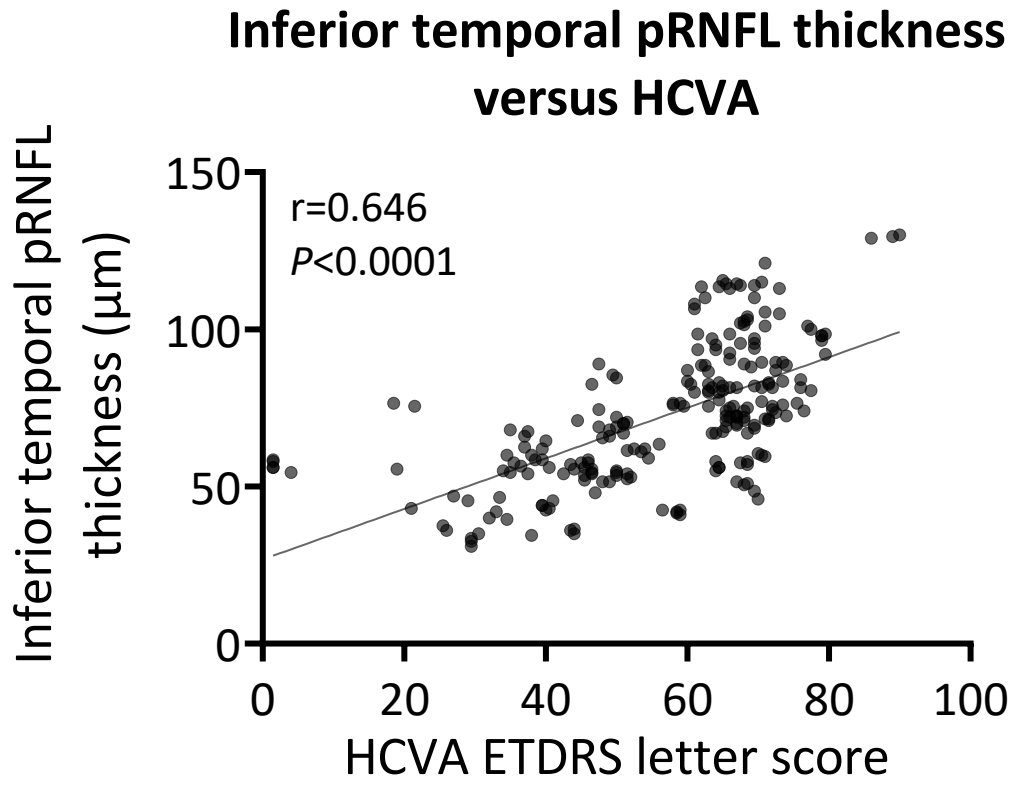
For all visits combined, temporal pRNFL thickness was associated with visual acuity in ADOA

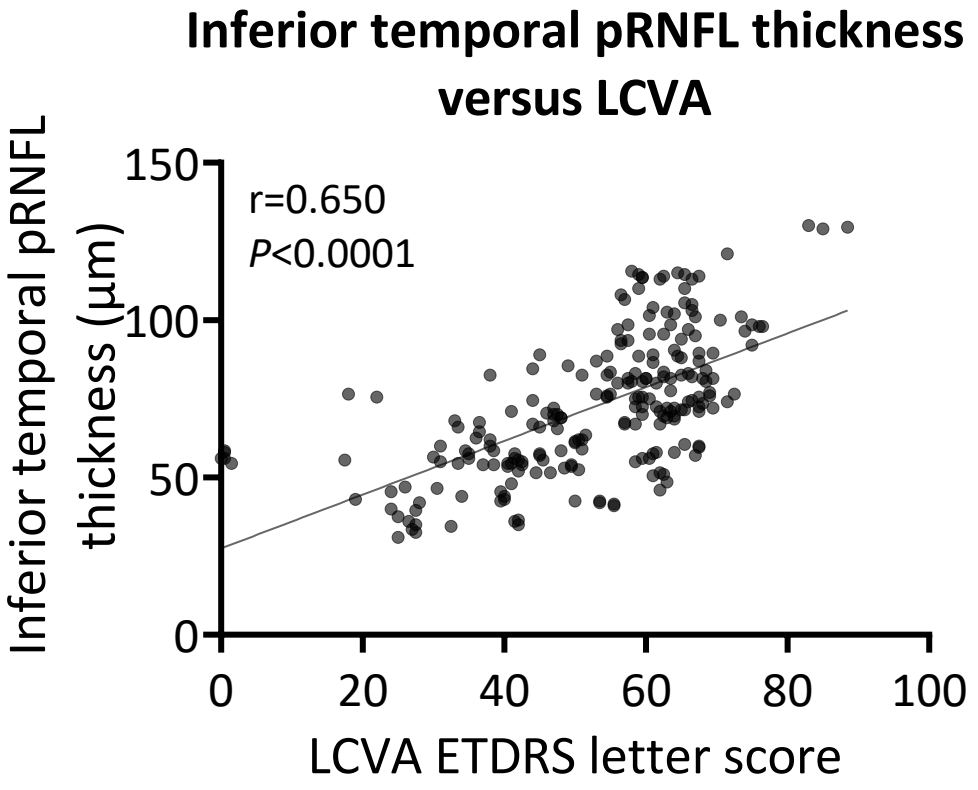




Month 24 data cut: July 11, 2025. Spearman rank-order correlations and *P*-values are reported. Patient sample size: N=47 for both correlations. Total visits plotted: n=226 for the correlation between temporal pRNFL thickness and HCVA ETDRS letter score and n=224 for the correlation between temporal pRNFL thickness and LCVA ETDRS letter score.
ADOA, autosomal dominant optic atrophy; ETDRS, Early Treatment Diabetic Retinopathy Study; HCVA, high-contrast visual acuity; LCVA, low-contrast visual acuity; pRNFL, peripapillary retinal nerve fiber layer.

For all visits combined, inferior temporal pRNFL thickness was associated with visual acuity in ADOA





Month 24 data cut: July 11, 2025. Spearman rank-order correlations and *P*-values are reported. Patient sample size: N=47 for both correlations. Total visits plotted: n=226 for the correlation between inferior temporal pRNFL thickness and HCVA ETDRS letter score and n=224 for the correlation between inferior temporal pRNFL thickness and LCVA ETDRS letter score.
ADOA, autosomal dominant optic atrophy; ETDRS, Early Treatment Diabetic Retinopathy Study; HCVA, high-contrast visual acuity; LCVA, low-contrast visual acuity; pRNFL, peripapillary retinal nerve fiber layer.

Key findings

1. Although ADOA progresses slowly, measurable declines in LCVA can be detected over 24 months

2. The decline in LCVA over 24 months in the absence of changes in retinal anatomy suggests that short-term declines in LCVA may reflect reversible cellular dysfunction

3. Correlations between pRNFL thickness and visual acuity support the relationship between neural integrity and functional impairment

4. The data from the FALCON study support LCVA as a sensitive, clinically meaningful endpoint for detecting potential treatment efficacy in ADOA

ADOA, autosomal dominant optic atrophy; LCVA, low-contrast visual acuity; pRNFL, peripapillary retinal nerve fiber layer.

Thank you for your attention