FALCON: A Prospective Natural History Study of Patients with OPA1-Autosomal Dominant Optic Atrophy (ADOA)

#5117

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Disclosures: [1]Stoke Therapeutic employees; *Stoke Therapeutic clinical investigator

FALCON

INTRODUCTION

- ADOA is the most common inherited neuro-ophthalmic disorder
- Patients typically present in the 1st decade of life and >1/2 of all patients are registered legally blind by the 5th decade
- Most cases are caused by a heterozygous nuclear gene *OPA1* mutation, often leading to OPA1 protein haploinsufficiency
- This is associated with impaired mitochondrial function in retinal ganglion cells leading to apoptosis causing progressive and irreversible vision loss
- To date, no long-term prospective data on ADOA natural history are available

OBJECTIVES

- Provide multimodal functional and structural assessments of a OPA1 study cohort to expand ADOA phenotypic characterization
- Evaluate and compare functional and anatomic markers of ADOA progression
- Inform design, assessments, and endpoints for potential studies of STK-002

STUDY DESIGN

- **10 sites:** 5 US, 2 Italy, 2 UK, 1 Denmark
- **Enrollment:** 48 patients aged ≥8 to ≤60y, 3 age cohorts (8-17, 18-40, 41-60y) **FULLY ENROLLED**
- **Duration:** 24 months; assessments at baseline, 6, 12, 18, and 24 months
- **Primary endpoints:** Change from baseline to 24 months in visual acuity chart (ETDRS) best corrected visual acuity (BCVA), Humphrey Visual Field, retinal nerve fiber layer (RNFL), optical coherence tomography (OCT), macular ganglion cell layer/inner plexiform layer (GCL/IPL) thickness
- **Exploratory endpoints:** Retinal mitochondrial dysfunction were imaged with the Beacon
- **Key inclusion criteria:** ADOA clinical diagnosis with confirmed heterozygous *OPA1* variant, ≥5 ETDRS
- **Key exclusion criteria:** Gain-of-function or compound heterozygous *OPA1* variants, extraocular phenotypic manifestations of (syndromic) ADOA (ADOA-plus)

DEMOGRAPHICS

	8-17y (n=16)	18-40y (n=22)	41-60y (n=10)	Total (N=48)
Mean (SD) age at screening	13.3 (2.98)	28.8 (6.51)	49.0 (5.75)	27.8 (14.01)
Median	14.0	29.5	49.0	26.5
Min-Max	8-17	18-40	41-59	8-59
Sex Female: n (%)	9 (56.3)	8 (36.4)	5 (50.0)	22 (45.8)
BCVA – Snellen: Mean (rounded)	20/63	20/50	20/159	20/80
Min-Max	20/37-20/159	20/16-20/182	20/43-20/834	20/16-20/834
OPA1 Genotype				n (%)
Nonsense, deletion or splice site mutation with predicted loss of function				41 (85.42%)
Missense				5 (10.42%)
Missense / splice region / uncertain significance				1 (2.08%)
Elongated protein (Frameshift in last coding exon–new stop codon altering last 18 amino acids)				1 (2.08%)
TOTAL				48 (100%)

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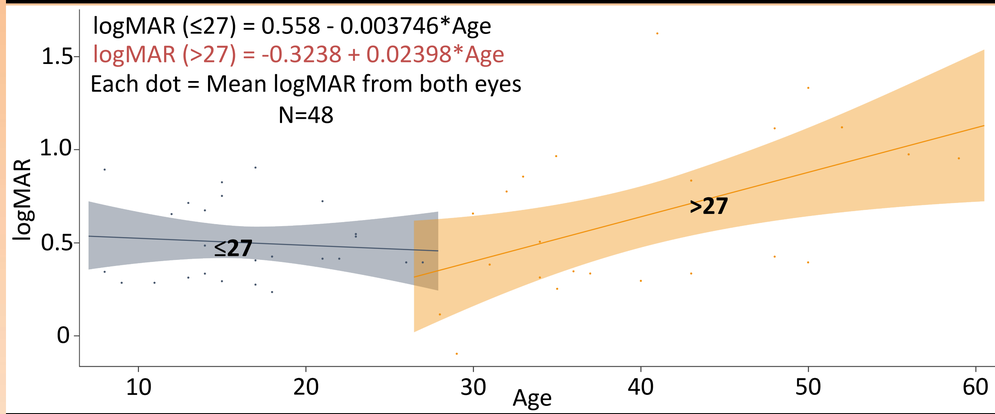
GCL/IPL and RNFL THICKNESS

Citation (N=ADOA Patients)	Mean GCL/IPL (µm)	Mean RNFL (µm)	Temporal RNFL (µm)
Barboni 2011 (N=33)		60.1 - 62.2	32.5 - 34.3
Barboni 2014 (N=39)	49.6 - 58.6	46.7 - 61.4	25.6 - 31.8
Corajevic 2018 (N=39)	41.9 - 45.5	48.8 - 114.2	3.7 - 56.9
Yu-Wai-Man 2011 (N=40)		54.1	33.4
FALCON (N=48)	45.5 - 51.3	54.9 - 69.0	27.2 - 30.7

Barboni et al. Am J Ophthalmol 2011; Barboni et al. Ophthal 2011; Corajevic et al. Acta Ophthalmol 2018; Yu-Wai-Man et al. Prog Ret & Eye Res 2011.

VISUAL ACUITY BY AGE



BCVA IN PATIENTS VS HISTORICAL CONTROLS OR MS PATIENTS

Assessment	logMAR Mean				Visual Accuity		
	<0.3 20/32 (n=9)	0.3-0.6 20/50 (n=20)	>0.6-0.9 20/118 (n=12)	>0.9 20/283 (n=7)	Controls 1 *Normal (N=211)	Controls 2 **Normal (N=90)	MS Patients Normal (N=130)
HC BCVA	74	65	47	27	87	98	74
2.5% LC BCVA	41	30	13	6	67	75	41
Difference (DELTA Letter Score: HC-2.5% LC)	**33**	**35**	**34**	**21**	**20**	**23**	**33**

- DELTA high contrast (HC)-2.5% low contrast (LC) letter score 10-15 letters higher than historical controls and similar to Multiple Sclerosis (MS) patients
- Higher DELTA in presence of 'disease' – both ADOA and MS

*Little et al. Invest Ophth Vis Sci 2013; **Balcer et al. Neuro 2003; logMAR values normalized to 100 Letter Scale; BCVA: best corrected visual acuity

SUMMARY AND FUTURE DIRECTIONS

- Low percentage of missense mutations (in part due to exclusion of ADOA plus)
- Patients with ADOA have profound deficits in visual function and disease worsens with age
- BCVA (HC and LC) was correlated to Humphrey 10-2 Mean Deviation, RNFL, and GCL/IPL thickness
- Difference between HC and 2.5% LC BCVA exceeded published historical control data by 10-15 letters suggesting large disease burden
- High assessment completion rates and relatively low intra-patient variability indicate reliability and potential repeat use, as would be required in ADOA interventional clinical studies
- 2-year follow-up of FALCON patients will provide valuable information on disease progression
- Currently, there is no approved treatment for people living with ADOA
- OSPREY interventional Phase 1 trial for STK-002 planned for 2024

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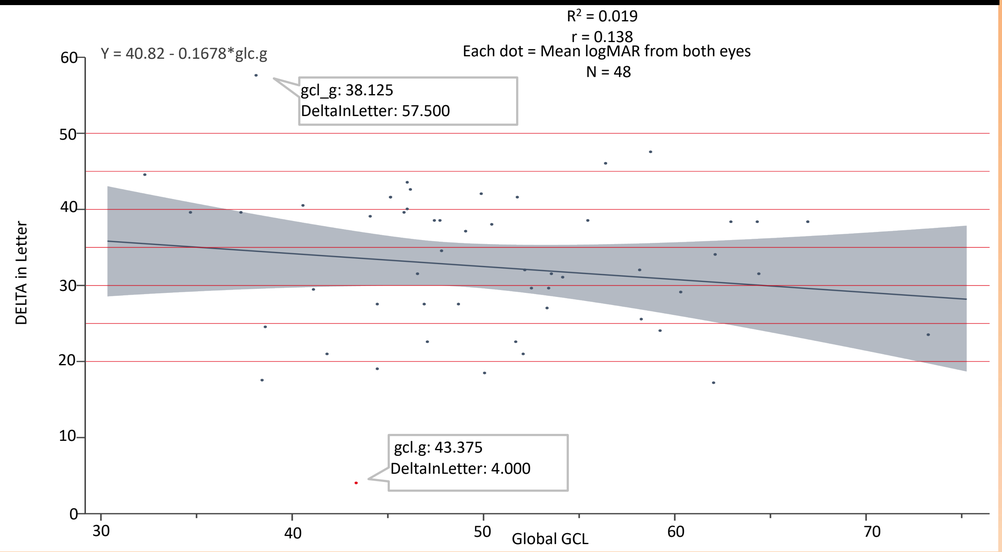
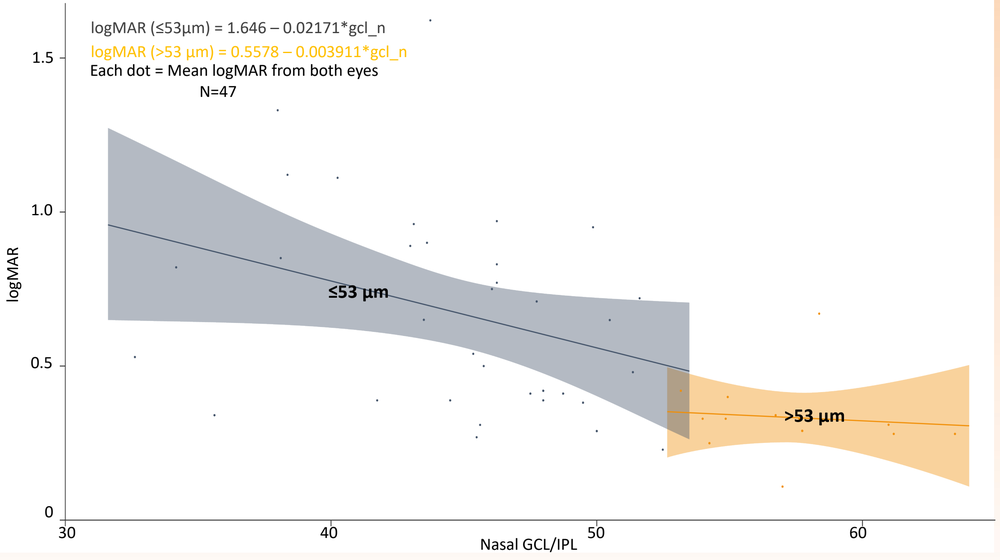
FALCON

HC MINUS LC BCVA (2.5%) (DELTA LETTER) GLOBAL GCL/IPL



VISUAL ACUITY VS GCL/IPL



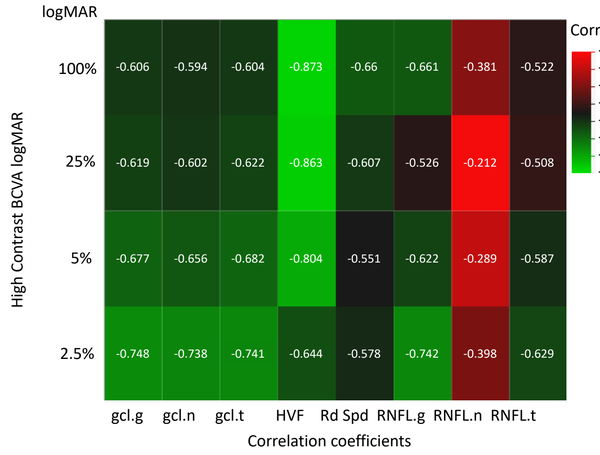
AGE VS FUNCTIONAL AND STRUCTURAL PARAMETERS

Functional Parameters	Mean (SD)
VF (10-2) MD	-1.897 (3.4714)
	-1.222 (2.9424)
	-11.08 (7.5227)
VF (10-2) PSD	4.645 (3.7914)
	3.766 (3.4642)
	9.806 (3.5912)
Reading Speed	115.8 (46.24)
	141.9 (33.79)
	79.63 (45.303)

Structural Parameters	Mean (SD)		Mean (SD)
GCL/IPL Nasal	50.67 (8.174)	RNFL Nasal	62.29 (11.303)
	49.05 (8.699)		56.27 (14.424)
	45.17 (5.795)		52.55 (14.700)
GCL/IPL Temporal	51.86 (9.000)	RNFL Temporal	30.71 (6.659)
	50.04 (7.981)		30.48 (8.692)
	44.94 (5.526)		27.15 (3.881)
GCL/IPL Global	51.26 (8.514)	RNFL Global	69.04 (11.669)
	49.55 (8.227)		65.18 (13.201)
	45.05 (5.615)		54.90 (8.212)

8-17y
18-40y
41-60y

HC/LC VISUAL ACUITY VS FUNCTIONAL and ANATOMIC PARAMETERS



Highly correlated:

- logMAR 2.5% with Global, Nasal, and Temporal GCL, and Global RNFL
- logMAR/Low Contrast logMAR with Humphrey (HVF 10-2)

Weakly correlated or confounded (data not shown):

- Global and Nasal GCL/IPL to Age
- Global RNFL to Age
- logMAR BCVA vs duration of ADOA symptoms- not useful due to diagnosis variability
- Read Speed (Rd Spd)- confounded by children's age, thus not useful

HUMPHREY VISUAL FIELD VS AGE