HTA 15.09.10 Supplementary file 1. Treatments for Stargardts disease

Röck et al

Study details	**Participant details**
Rock T, Schatz A, Naycheva L, Gosheva M, Pach J, Wilhelm B, et al. Effects of transcorneal electrical stimulation in patients with Stargardt's disease. [German, English]. Ophthalmologe 2013;110:68-74. Rock T, Schatz A, Naycheva L, Willmann G, Bartz-Schmidt K-U, Zrenner E, et al. Effects Of Transcorneal Electrical Stimulation In Patients With Stargardt Disease - A Prospective, Randomized, Sham-controlled Pilot Study. Investigative Ophthalmology & Visual Science 2011;52:1870 *Country:* Germany *Design:* RCT *Number of centres:* 1 *Funding:* Okuvision GmbH, Reulingen *Trial ID:* NCT00804102	*Number of Participants*: total 12, 66% TES 4; 150% TE 4; Sham 4 *Number of eyes* 12, 66% TES 4; 150% TE 4; Sham 4 *Sample attrition/dropout*: none *Sample crossovers:* none *Inclusion criteria:* Stargardt's disease, age >18 years, visual acuity 0.02 to 0.9, evaluable full field ERG, multifocal ERG and static visual field; eye with worse visual acuity was selected(appears to be a subgroup of a larger study for those with various retinal diseases) *Exclusion criteria:* other eye diseases (e.g. advanced diabetic retinopathy, choroidal neovascularisation, exudative age-related macular degeneration), silicone oil tamponade, serious other diseases aged >99 years

Intervention details	**Outcomes**
Intervention *1.* Sham-stimulation *2.* Transcorneal electrical Stimulation (TES) with 66% of the individual electrically stimulated phosphene threshold *3.* TES Stimulation with 150% of the individual electrically stimulated phosphene threshold *Dose details:* modified neurostimulator with rectangular biphasic pulses (5 ms positive, directly followed by 5 ms negative) at 20 Hz; the threshold current for triggering phosphenes was determined for every patient several times at every visit by reduction of the current when phosphenes were certainly observed until they disappeared as well as increase of a low current until phosphenes were observed; an arithmetic mean of the thresholds was derived; threshold determination took place in a completely darkened room; the threshold that was determined in this way before every 30 min stimulation served to determine the individual current of stimulation in the respective study arm (0, 66% or 150% of the phosphine threshold); after determination of the threshold the light in the room was switched on so that participants of the 150% group could not detect whether they were stimulated; for; for the sham stimulation the threshold was determined without activating the electrical stimulation *Dose modifications:* not reported *Concurrent treatment:* not reported	*Outcomes (state if primary)* visual acuity (EDTRS), phosphine threshold, visual field mean defect, optical coherence tomography BCVA Electroretinography (not extracted) Electrically evoked phosphene threshold (not extracted) Adverse events *Length of follow-up:* 8 weeks (? Not clear), 9 measurements: baseline, weekly measurements during stimulation period (measurements 2-7), 2 follow-up visits

Duration of treatment: 30 minutes once per week for 6 consecutive weeks	

Participant characteristics, %				
	Sham, n=4	**TES 66%, n=4**	**TES 150% n=4**	**P value**
Age, years mean (SD)	All: 40.0 SD9.07 years			
Sex, % male	NR	NR	NR	
Ethnic origin *% White*	NR	NR	NR	
Classification	NR	NR	NR	
Smoking history	NR	NR	NR	
visual acuity, mean (SD)	0.74 (0.25)	0.65 (0.24)	0.88 (0.79)	NR
BCVA, range 0.04 – 0.7				
lesion size	NR	NR	NR	
previous treatments	NR	NR	NR	
Key comorbidities	NR	NR	NR	
Family history	NR	NR	NR	
Comments				
	Results			
	Sham, n=4	**TES66%, n=4**	**TES 150% n=4**	**P Value**
EDTRS (last visit) (SD)	0.66 (0.21)	0.45 (0.21)	0.63 (0.55)	
Mean intraindividual changes were to be 0.06 for Sham, 0.14 for 66% and 0.19 for 150% groups respectively (p=0.66).				
BCVA change, logMAR, mean (SE)	-0.03 (0.01)	-0.03 (0.01)	0.02 (0.01)	0.07
Comments				
Outcome 3				
Comments				
Adverse events	0	0	0	
Comments no adverse effects in any of the groups				

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	unclear	method not reported
Allocation concealment (selection bias)	unclear	method not reported
Blinding participants and personnel (performance bias), Objective outcomes	unclear	patients blinded, person carrying out intervention not blinded
Blinding participants and personnel (performance bias), Subjective outcomes	no subjective outcomes	
Blinding outcome assessors (detection bias), Objective outcomes	unclear	outcome assessor not blinded for measurement of visual acuity, outcome assessors blinded for ERG and visual field measurements
Blinding outcome assessors (detection bias), Subjective outcomes	no subjective outcomes	
Incomplete outcome data (attrition bias), Objective outcomes	low	no drop-outs
Incomplete outcome data (attrition bias), Subjective outcomes	no subjective outcomes	
Selective reporting (reporting bias)	low	outcomes reported as stated in methods
Other biases	low	No other apparent biases

Kondrot et al

Study details	Participant details
Kondrot EC. Improvement in Vision Parameters for Participants Treated With Alternative Therapies in a 3-day Program. Alternative Therapies in Health & Medicine 2015;21:22-35 *Country:* USA *Design:* retrospective before-and-after study (data collected over 10 years) *Number of centres:* one *Funding:* No external funding. Participants paid $3000 each. *Trial ID:* Not reported	*Number of Participants*: Total 152. Dry AMD 70, Stargardt's disease 3 (79 with other eye diseases, not extracted) *Number of eyes:* Total 290. Dry AMD 140, Stargardt's disease 6 (144 with other eye diseases, not extracted) *Sample attrition/dropout*: Not reported *Sample crossovers:* Not reported *Inclusion criteria:* eye disease not responsive to traditional treatments, patients wanted to avoid surgery or side effects of medication, paid $3000 for 3-day treatment programme. *Exclusion criteria:* Not reported

Intervention details	Outcomes
Intervention 1. Customised, Intravenous nutrition (Myer's cocktail), oxidative therapy, microcurrent stimulation, syntonic light therapy (all provided at least one to each participant) *Dose details:* Myer's cocktail: accorbic acid 600 mg/ml, 1cc; pyridoxine 100mg/ml 2cc; hydroxocobalamin 1000 ug/ml 1cc; B complex 100, 1cc; calcium gluconate 10% 1 cc; dexpanthenol 250 mg/ml, 1 cc; magnesium chloride 200 mg/ml, 1 cc; multitrave-5 concentrate 1cc; selenium 40 ug/ml 5cc; taurine 50 mg/ml 2cc; zinc 1 mg/ml 5cc; lidocaine 2% 5cc; sterile water 200cc; folic acid 1 mg. Oxidative therapy: minimum of 2 intravenous therapies. Ozone was mixed with blood and injected into body and provided as eye drops (no further details) Intravenous hydrogen peroxide given to some patients. Microcurrent stimulation: no details of frequency or duration of application Syntonic light therapy: 2 treatments per day *Dose modifications:* Not reported *Concurrent treatment:* Information about diet, nutrition, hydration and creation of balance in autonomic nervous system. Homeopathy prescribed but not started during 3 day programme. *Duration of treatment:* 3 days programme (microcurrent therapy initiated on day 2)	*Outcomes (state if primary)* Visual acuity (ETDRS), contrast sensitivity, campimetry, pursuits, saccade and fixation tests, pupillary examination, external examination of eye, anterior segment examination, intra-occular pressure, dilated examination of eye. Selected outcomes for some participants: ocular coherence tomography, infrared thermography, heavy-metal toxicity in urine, oxygen saturation at night *Length of follow-up:* 3-days (not clear)

ETDRS: Early Treatment Diabetic Retinopathy

Participant characteristics, %
Not reported per eye disease. For the total 152 participants:

Age, years range	15-95		
Sex, % male	48		
Results			
	Dry AMD, n=70 (140 eyes)	**Stargardt's disease, n=3 (6 eyes)**	**P Value**
Acuity improvement, ETDRS chart, mean; n (%) *> 2 lines (10 letters)* *1-2 lines (5 letters)* *< 1 line* *No change*	Mean 5.5 letters 22 eyes (15.7) 53 eyes (37.9) 50 eyes (35.7) 15 eyes (10.7)	Mean 6.6 letters (range 2-13)	
Contrast improvement mean; n (%) *>6 letters* *3-5 letters* *1-2 letters* *No change*	Mean 3.8 letters 35 eyes (25.0) 38 eyes (27.1) 54 eyes (38.6) 13 eyes (9.3)	Mean 3.67 letters (range 0-10)	
Visual field expansion, n (%) *Marked* *Moderate no change or minimal*	 76 eyes (54.3) 41 eyes (29.3) 23 eyes (16.4)	 6 eyes (100) 0 eyes 0 eyes	
Comments			
Adverse events			
Not reported			

Before-After (Pre-Post) Studies With No Control Group

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	x		
2. Were eligibility/selection criteria for the study population prespecified and clearly described?		x	
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?		x	
4. Were all eligible participants that met the prespecified entry criteria enrolled?			CD
5. Was the sample size sufficiently large to provide confidence in the findings?	x	x	(yes For Dry AMD)
6. Was the test/service/intervention clearly described and delivered consistently across the study population?		x	
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?			CD
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?		x	
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?			CD
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?		x	
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?		x	
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?			NA

Quality Rating Poor
Additional Comments: population not predefined or described; few details of intervention or outcomes; no statistical analysis; unclear duration of follow-up

*CD, cannot determine; NA, not applicable; NR, not reported

Teussink et al

Study details	**Participant details**
Teussink MM, Lee MD, Smith RT, van Huet RA, Klaver CC, Klevering BJ, et al. The effect of light deprivation in patients with Stargardt disease. American Journal of Ophthalmology 2015;159:964-72.e2. *Country:* The Netherlands *Design:* Case series *Number of centres:* one *Funding:* non-commercial *Trial ID:* not reported	*Number of Participants*: total 5 *Number of eyes* total 5 *Sample attrition/dropout*: none *Sample crossovers:* not applicable *Inclusion criteria:* Stargardt disease, at least 1 ABCA4 mutation, typical clinical symptoms associated with Stargardt's retinal dystrophy. Best eye included. *Exclusion criteria:* any medical concerns regarding the use of contact lenses

Intervention details	**Outcomes**
Intervention *1.* Light exposure protection *Dose details:* best eye had a black contact lens which covered the entire cornea and blocked >90% of light in the visible spectrum. *Dose modifications:* not reported *Concurrent treatment:* were previously advised of the potential benefits of wearing sunglasses, avoiding direct light exposure, and limiting dietary intake of vitamin A. Complete protection from light exposure was suggested as a treatment option. *Duration of treatment:* worn for waking hours for a year	*Outcomes (state if primary)* BCVA Fundus autofluorescence (not extracted) Compliance Adverse events Presence of geographic atrophy *Length of follow-up:* 17.8 months (range 11-26)

Participant characteristics, %			
	Light protection, n=5		**P value**
Age, years mean (SD)	22.6 (range 10-46)		
Sex, % male	40		
Ethnic origin *% White*	100		
BCVA treated eye, no mean value provided Pt 1 Pt 2 Pt 3 Pt 4 Pt 5	 20/40 20/12.5 20/400 20/125 Finger counting		
Results			
	Light protection, n=5		**P Value**
BCVA treated eye, no mean value provided Pt 1 Pt 2 Pt 3 Pt 4 Pt 5	 20/100 20/20 20/400 20/125 Finger counting		
Comments: states that BCVA was stable in all but patient 1 during the study period.			
Presence of geographic atrophy	0		

Adverse events	0		
Bilateral nuclear cataract, n	1		
Comments States treatment compliance was reported in all participants, no further details.			

Case series studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	x		
2. Was the study population clearly and fully described, including a case definition?		x	
3. Were the cases consecutive?		x	
4. Were the subjects comparable?			CD
5. Was the intervention clearly described?	x		
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?		x	
7. Was the length of follow-up adequate?	x		
8. Were the statistical methods well-described?			NA
9. Were the results well-described?		x	

Quality Rating: Poor
No mean values reported, no description of visual acuity measures, unclear if participants were comparable as few characteristics reported, selected patients who requested any treatment

*CD, cannot determine; NA, not applicable; NR, not reported

Schwartz et al

Study details	Participant details
Schwartz SD, Regillo CD, Lam BL, Eliott D, Rosenfeld PJ, Gregori NZ, et al. Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies. Lancet 2015;385:509-16. Schwartz SD, Tan G, Hosseini H, Nagiel A. Subretinal Transplantation of Embryonic Stem Cell-Derived Retinal Pigment Epithelium for the Treatment of Macular Degeneration: An Assessment at 4 Years. Investigative Ophthalmology & Visual Science 2016;57:ORSFc1-9. *Country:* USA *Design:* 2 before-after studies *Number of centres:* 4 *Funding:* Supported by Ocata Therapeutics and an unrestricted grant from Research to Prevent Blindness, the Price Foundation, UCLA Broad Stem Cell Research Center, and the Stein Eye Institute Clinical Research Center, UCLA Department of Ophthalmology. Funder of the study participated in the study design, data gathering, analysis, and interpretation, and writing of the report.	*Number of Participants*: Study 1: n= 9 with dry AMD Study 2: n=9 with Stargardt's macular dystrophy (STGD) *Number of eyes:* Study 1: 9 eyes (eye with worst vision) Study 2: 9 eyes (eye with worst vision) *Sample attrition/dropout*: Not stated *Sample crossovers:* Not applicable *Inclusion criteria:* AMD: age >55 years, advanced dry AMD with >250 microns of geographic atrophy involving central fovea or STGD: age > 18 years, end-stage disease, peripheral visual field constriction. Both diseases: BCVA of study eye 20/400 or worse; BCVA of fellow eye 20/400 or better, the ability to undergo a vitreoretinal surgical procedure under monitored anesthesia care, and psychological suitability to participate in a first-in-human clinical trial involving hESC-derived cells *Exclusion criteria:* other significant ophthalmic pathology, history of cancer, contraindications for systemic immunosuppression. Further details given in study appendix (not extracted).

Trial ID: NCT01345006 (STGD) and NCT01344993 (dry AMD).	
Intervention details	**Outcomes**
Intervention 1. Subretinal transplantation of hESC derived retinal pigment epithelium (RP) *Dose details:* Injected 150 lL of resuspended hESC-RPE. Three dose cohorts were used for each disorder with each cohort comprising three patients with STGD and three with AMD: cohort 1 received 50,000 cells, cohort 2 received 100,000 cells, and cohort 3 received 150,000 cells. *Dose modifications:* Not reported. *Concurrent treatment:* The immunosuppression regimen included tacrolimus (target blood concentrations 3–7 ng/mL) and mycophenolate mofetil (ranging from 0.25–2.00 g orally per day) a week before the surgical procedure and continued for 6 weeks. At week 6 the regimen called for discontinuation of tacrolimus and a continuation of mycophenolate mofetil for an additional 6 weeks. *Duration of treatment:* Single treatment with 12 weeks of immunosuppression.	*Outcomes (state if primary)* Safety and tolerability (primary outcome); best-corrected visual acuity (ETDRS) , visual fields, slit-lamp biomicroscopy, ophthalmoscopy, OCT, fluorescein angiography, autofluorescence, fundus photography, electroretinography and systemic monitoring (i.e. serial physical examinations, vital signs, electrocardiograms, cancer screening, and hematological and serological testing); and, quality of life. *Length of follow-up:* Median follow-up 22 months (4 patients had <12 months follow-up, 12 patients had 12–36 months follow-up, and 2 patients had >36 months follow-up)

Participant characteristics, %			
	Dry AMD, n=9	**STGD, n=9**	**P value**
Age, years median (range)	77 (70-88)	50 (20-71)	Not reported
Sex, % male	33.3	44.4	Not reported
Ethnic origin *% White*	100	88.9	Not reported
*visual acuity (*BCVA ETDRS)	Ranged from 20/200 (severe vision loss) to hand motion (near blindness)	Ranged from 20/200 (severe vision loss) to hand motion (near blindness)	Not reported
Results			
	Dry AMD, n=9	**STGD, n=9**	**P Value**
Adverse events from cellular therapy	0	0	
Adverse events from surgical procedure and systemic immunosuppression	See comments	See comments	
Any serious adverse event (system organ classification)	4 (Infections: 1; injury: 1; neoplasms: 1; nervous system disorders: 2; psychiatric disorders: 1)	2 (General disorders: 1; Infections: 1)	

Systemic adverse events likely related to immunospression, system organ classification:			
Cardiovascular	0	1	
Central nervous system	7	8	
Gastrointestinal	16	6	
General	6	2	
Genitourinary	0	1	
Haematology	4	0	
Infection	6	2	
Metabolic	3	1	
Musculoskeletal	2	0	
Psychiatric	1	0	
Respiratory	3	1	
Skin	2	0	
Comments: Adverse events - cellular therapy: None of the eyes exhibited any sign of acute transplant rejection (e.g. prominent lymphocyte infiltration, acute or chronic uveitis, or cystoid macular edema) or hyperproliferation, teratoma formation, or apparent dedifferentiation of the cells. Angiographic analysis revealed no abnormalities in the retinal vascular or choroidal circulations up to 1 year after surgery. Adverse events - surgical procedure and the systemic immunosuppression: 3 eyes had preretinal pigmented foci visible on biomicroscopy and OCT near the injection site; 0 eyes had epiretinal membrane formation or hyperproliferation resulted from these foci; 4 eyes developed worsening cataracts requiring cataract surgery (1 AMD; 3 STGDs); 1 eye had culture positive acute postoperative endophthalmitis (Staphylococcus epidermidis) in STGD patient; 0 eyes had subretinal inflammation; 1 eye developed vitreous inflammation with an inferior transvitreal band. Other treatment related adverse events (immunosuppression): 1 patient had a urinary tract infection that necessitated discontinuation of the immunosuppression; several patients had gastrointestinal symptoms;2 patients had nonmelanoma skin cancers.			
Visual acuity (ETDRS) (6 months) (i) improved by:	Dry AMD (9 eyes)	STGD (8 eyes)	Not reported
≥15 letters	4 eyes	3 eyes	
11-14 eyes	2 eyes	0 eyes	
≤10 letters (stable)	3 eyes	4 eyes	
(ii) worsened			
11 letters	0 eyes	1 eye	
Visual acuity (ETDRS) (12 months) improved by:	Dry AMD (7 eyes)	STGD (7 eyes)	Not reported
≥15 letters	3 eyes	3 eyes	
11-14 eyes	1 eye	0 eyes	
≤10 letters (stable)	3 eyes	3 eyes	
(ii) worsened			
10 letters	0 eyes	1 eye	
The National Eye Institute Visual Function Questionnaire 25 (Quality of life), change from baseline at 12-52 weeks post transplant, median:			
General vision	Baseline: 40.0 12-52 wks: 20.0	Baseline: 30.0 12-52 wks: 20.0	
Peripheral vision	Baseline: 50.0 12-52 wks:25.0	Baseline: 75.0 12-52 wks: 12.5	
Near activities	Baseline: 20.8 12-52 wks: 25.0	Baseline: 33.3 12-52 wks: 8.3	
Distance activities	Baseline: 37.5 12-52 wks: 16.7	Baseline: 33.3 12-52 wks: 12.5	
Mental health	Baseline: 37.5 12-52 wks: 18.8	Baseline: 56.3 12-52 wks: 9.4	

Subgroups	*Untreated*	*Treated*	
Median (IQR) change in VA in eyes of patients with dry AMD that did not develop cataracts during at least 6 months of follow-up:	Dry AMD - untreated eye (n=8)	Dry AMD - treated eye (n=8)	At 12 months: p=0.0117, Wilcoxon signed-rank, two-tailed test.
1 month	6 letters (-3.5 to 10.9)	13 letters (3.8 to 31.8)	
3 months	6 letters (-1.5 to 8.7)	14 letters (5.5 to 23.8)	
6 months	-1 letters (-1.0 to -6.0)	16 letters (4.3 to 18.8)	
12 months	-1 letters (-5.0 to 6.1)	14 letters (3.0 to 19.0)	
Median (IQR) change in VA in eyes of patients with dry AMD that did not develop cataracts during at least 6 months of follow-up:	STGDs - untreated eye (n=5)	STGDs - treated eye (n=5)	At 12 months Wilcoxon signed-rank, two-tailed test not calculated due to small sample
1 month	4 letters (-0.5 to 12.0)	10 letters (-4.5 to 14.0)	
3 months	4 letters (-0.5 to 11.5)	14 letters (-3.5 to 16.0)	
6 months	4 letters (-1.0 to 9.5)	15 letters (-2.0 to 17.0)	
12 months	2 letters (-1.5 to 12.0)	12 letters (-2.5 to 21.0)	
	Dry AMD	**STGDs**	
Median difference in change from baseline in VA at 12 months between treated and untreated eyes that did not develop cataracts or have ocular surgery during follow-up for different dosages.	Dry AMD	STGDs	Not reported
Cohort 1 (50 000 cells)	8 letters (range 4–23) (n=3)	9 letters (range 9–9) (n=3)	
Cohort 2 (100 000 cells)	8 letters (range 2–14) (n=2)	2 letters (n=1)	
Cohort 3 (150 000 cells)	15 letters (range 13–44) (n=3)	5 letters (range 0–10) (n=2)	

Before-After (Pre-Post) Studies With No Control Group

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	y		
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	y		
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?			CD
4. Were all eligible participants that met the prespecified entry criteria enrolled?			CD
5. Was the sample size sufficiently large to provide confidence in the findings?		n	
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	y		
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	y		
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?		n	
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	y		
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	y		For some outcomes only
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-		n	

series design)?			
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?			NA

Quality Rating: Fair

*CD, cannot determine; NA, not applicable;NR, not reported

Aleman et al

Study details	**Participant details**
Aleman TS, Cideciyan AV, Windsor EA, Schwartz SB, Swider M, Chico JD, et al. Macular pigment and lutein supplementation in ABCA4-associated retinal degenerations. Investigative Ophthalmology & Visual Science 2007;48:1319-29 *Country:* USA *Design:* Before-after study, no control (pilot) *Number of centres:* assume one *Funding:* not reported *Trial ID:* Non-commercial funding	*Number of Participants*: Total 11 (10 analysed: 8 Stargardt, 2 cone-rod dystrophy) (compared with 8 healthy controls, not extracted) *Number of eyes* 16 analysed *Sample attrition/dropout*: 1 excluded due to no serum response to lutein *Sample crossovers:* Not applicable *Inclusion criteria:* Stargardt disease or cone-rod dystrophy with foveal fixation and known or suspected disease-causing mutations in the ABCA4 gene; relatively spared foveal function in at least one eye. *Exclusion criteria:* No additional criteria stated.

Intervention details	**Outcomes**
Intervention *1.* Lutein *Dose details:* Oral lutein supplementation 20mg /day *Dose modifications:* Not reported *Concurrent treatment:* Not reported *Duration of treatment:* 6 months	*Outcomes (state if primary)* Macular pigment (not extracted) Macular pigment optical density (MPOD) Absolute dark-adapted sensitivity (not reported) Serum lutein and zeaxanthin levels (not extracted) *Length of follow-up:* 6 months

Participant characteristics, %			
	Lutein, n=11		**P value**
Age, years mean (SD)	30 (11)		
Sex, % male	64		
Ethnic origin *% White*	 82		
Classification, % *Stargardts* cone-rod dystrophy	 73 27		
Smoking history, % *smoker*	 27		
visual acuity			
Foveal MPOD, mean (SD) 2° 5°	 0.17 (0.09) 0.11 (0.06)		
Foveal absolute sensitivity, dB, mean SD	26.2 (6.3)		
Results			
	Lutein, n=10		**P Value**

Foveal MPOD, mean (SD) 2° 5°	 0.28 (0.14) 0.18 (0.10)		
Comments: Change from baseline p<0.001 at 2° and 5°.			
States that parafoveal increases were not significant (data not reported).			
Foveal absolute sensitivity, dB, mean SD	26.0 (6.7)		
Comments States foveal absolute sensitivity as a measure of central visual function was little changed after supplementation, p value not reported.			
Mean change in foveal sensitivity, dB *Responder* *Non-responder* Responder vs non-responder	 -1.20 (2.5) 1.21 (2.7) p>0.05		
Mean change in LogMAR acuity *Responder* *Non-responder* Responder vs non-responder	 -0.02 (0.03) -0.02 (0.06) p>0.05		
Responders defined by the 95th percentile for differences between baseline MPODs at the two locations. Characteristics of Lutein responders vs non-responders compared, not extracted			

Before-After (Pre-Post) Studies With No Control Group

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	x		
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	x		
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?			CD
4. Were all eligible participants that met the prespecified entry criteria enrolled?		x	
5. Was the sample size sufficiently large to provide confidence in the findings?		x	
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	x		
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	x		
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?		x	
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	x		
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	x		
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?		x	
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?			NA

Quality Rating: Fair
Selected participants, small sample size

Querques et al

Study details	Participant details
Querques G, Benlian P, Chanu B, Leveziel N, Coscas G, Soubrane G, et al. DHA supplementation for late onset Stargardt disease: NAT-3 study. Clinical Ophthalmology 2010;4:575-80. *Country:* France *Design:* Case series *Number of centres:* one *Funding:* not reported *Trial ID:* not reported	*Number of Participants*: 20 *Number of eyes:* 40 *Sample attrition/dropout*: none *Sample crossovers:* not applicable *Inclusion criteria:* late onset Stargardt's disease (reported onset >18 years); >18 years old; evidence of hypo-autofluorescence from areas of macular atrophy, associated or not with retinal flecks; presence of hyperautofluorescent retinal flecks, associated or not with areas of macular atrophy; diagnosis of dark choroid on fluorescein angiography *Exclusion criteria:* not reported

Intervention details	Outcomes
Intervention *1.* docosahexaenoic acid (DHA) supplementation *Dose details:* 840 mg per day *Dose modifications:* not reported *Concurrent treatment:* not reported *Duration of treatment:* 6 months	*Outcomes (state if primary)* BCVA (ETDRS charts) Fundus autofluorescence (not extracted) Serum fatty acids (not extracted) Adverse events Progression in size of central atrophy Progression to choroidal neovascularization *Length of follow-up:* 6 months

Participant characteristics, %			
	DHA, n=20		**P value**
Age, years mean (SD)	45 (15)		
Sex, % male	55		
BCVA	Individual patient data only reported		
Results			
	DHA, n=20		**P Value**
BCVA change	Individual patient data only reported		
Comments: states no statistical differences at month 6 compared with baseline, p>0.05			
BCVA Mild improvement, % pts (eyes)	20 (7.5)		
Comments			
Progression in size of central atrophy	0		
Progression to choroidal neovascularization	0		
Adverse events	0		

Case series studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	x		
2. Was the study population clearly and fully described, including a case definition?	x		
3. Were the cases consecutive?			CD

4. Were the subjects comparable?			CD
5. Was the intervention clearly described?	x		
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
7. Was the length of follow-up adequate?	x		
8. Were the statistical methods well-described?	x		
9. Were the results well-described?		x	

Quality Rating:Fair