The Zeaxanthin and Atrophic AMD Visual Function Study (ZVF)- Investigator Initiated FDA IND #78,973 (Baseline Data)

S.P. Richer[1,3], W. Stiles[1], K. Graham[1], C. Thomas[1], L. Clouser1, J. Nyland[1], P. Touzeau[1], J. Bekritsky[1], D. Richer[2], D. Park[3]. [1]Eye Clinic 112E, DVA Medical Center, North Chicago, IL; [2]University of Pennsylvania, Philadelphia, PA; [3]RFUMS Chicago Medical School, North Chicago, IL.

INTRODUCTION

While some 5.5 million Americans with AMD are projected to require emergency pharmaceutical and surgical management to avoid catastrophic vision loss from neovascular AMD by the year 2050, ten times this number, or some 55 million Americans will develop less severe, but none-the-less visually disabling RPE / photoreceptor atrophy – characterized as mild and moderate AMD. (Ref 1 – in press)

Our group published 3 peer reviewed clinical trials (1996, 1999 & 2004), demonstrating visual function in atrophic AMD to be nutrition responsive. (Refs 2-9) Our 1996 Clinical Results demonstrated stabilization of visual function with multivitamins (without lutein) and were, in part, later validated by the AREDS 2001 National Eye Institute / NEI trial. Our 1999 two-part study provided a protocol for evaluation of atrophic AMD utilizing simple inexpensive tests such as the Amsler grid, Contrast Sensitivity Function (CSF), low luminance/contrast (SKILL) and a photographic light box - glare recovery measurement. (Ref 4) When used in an analogous fashion to a glaucoma workup (i.e. baseline and serial exams), this metric was useful for evaluating visual function in both incipient AMD (AREDS stage I and II retinal disease) as well as more advanced AMD (AREDS III and IV). (Ref 5) Case series experimentation with spinach consumption provided a basis for a formal double masked, randomized placebo controlled study with lutein and lutein/antioxidants and subsequent publication of the LAST Study in 2004 (Ref 7) and LAST II in 2007 (Ref 9).

AREDS II is concerned with prevention of catastrophic vision loss in high risk patients, while our research concerns the effect of carotenoids on visual function in mild and moderate AMD. Such visual function parameters may affect modern cultural vision (i.e. driving and reading) and ambulation which in turn have productivity and safety implications. Carotenoid research is also important, from a Preventive Medicine standpoint, in sub-populations with inadequate fruit and vegetable intake. Indeed the greatest rate of change (increase) in macular pigment occurs in subjects with lowest measured macular pigment (Ref 9).

AREDS II is also evaluating Zeaxanthin (ZX) at 2 mg per day. As ZX may be an even more important carotenoid than lutein due to foveal predominance, and its higher prevalence in the Asian diet, we have chosen to evaluate the effect of 8 mg per day on visual function, with and without lutein.

METHODS

Following FDA and DVA IRB/Human Subjects approval in early December 2007, some (n=53 patients) of 60 patients have completed the Informed Consent process, enrolled in ZVF, and completed their 1st Baseline Evaluation. We present available demographic, symptom, visual function and ocular descriptive data (i.e. mean, sd) on the entire sample population of subjects to date (n=53, 105 eyes). We also assess sample population visual/functional dependent variables with respect to MP (1 degree foveal macular pigment optical density). In this case, **R²** represents the "coefficient of determination" or "common variance". For example, if you were to predict foveal MP based upon visual acuity (near) you would be able to account for 16% of the variability seen in the pigment values. The "correlation coefficient" **r** is merely the square root of this variance value. See ABSTRACT for additional details.

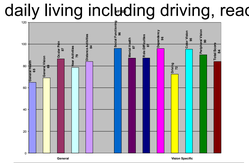
RESULTS

Demographics: Baseline population: age, gender, months since AMD diagnosis, smoking (packs/day), alcohol consumption in drinks/day, self described physical activity (5 levels), systemic state (CAD, HTN, DM) and observed Iris color (blue, green and brown).

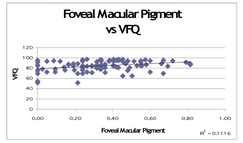
Age	74.5 sd 10.1			
Gender	51 males	2 females		
AMD diagnosed	48.8 mo			
Current Smokers	9 yes	44 no		
	1.1 ppd 1.1 ppd / 5 yrs			
ETOH Use	49 are drinkers 2.04 avg / day	14 no		
	1.99 avg / 5 yrs			
Physical activity	10 very light	15 light	24 moderate	4 strenuous
Systemic state	13 CAD	7 HTN	7 DM	
Iris color	30 Blue/Grey	11 Brown	12 Green/Hazel	

POPULATION Health Related Quality of Life VFQ 25 QUESTIONAIRRE

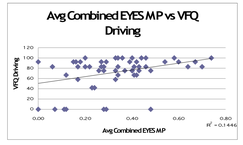
This NEI survey reveals visual functional impairment on a range of activities of daily living including driving, reading and watching TV.



This AMD population has less than ideal self-assessed health and driving difficulty. Note that these patients in general, are at less risk for catastrophic vision loss than high risk AREDS and AREDS II AMD patients, and have excellent visual acuity (see below). There was a weak correlation (r = 0.33) of global VFQ25 scores and driving subscale VFQ25 scores with foveal MP (r = 0.38), but no relationship with overall health (r = - 0.15).

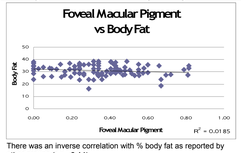


r = 0.33 indicating a correlation of MP (all eyes) with Global VFQ 25 composite scores.



r = 0.38 indicates higher MP was correlated with better driving - i.e. the better the measured average eye foveal MP, the better the VFQ25 driving subscale scores.

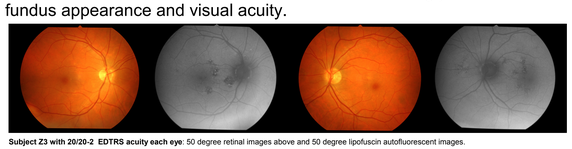
Body Mass Index (BMI) & Bioelectric Impedance



There was an inverse correlation with % body fat as reported by other groups (r = - 0.14).

The mean population BMI (Body Mass Index) was 29.3 (sd 4.9) indicating near- obesity, consistent with the literature. The mean population % BODY FAT was also elevated at 31.1 (sd 4.7). Note foveal MP (macular pigment optical density-see below) was not correlated with BMI in this population, but there was a weak expected inverse trend between % body fat and foveal MP (r = - 0.14) as reported by other groups.

50 degree Macular Photography and lipofuscin imaging Baseline and final (12 month) photographs are AREDS graded by a retinal specialist (ML). The camera is a Kowa Digital VK2 ® system (Kowa Optimed, Japan). Lipofuscin imaging is also accomplished with a high output flash combined with a 580nm exciter filter and a 660 nm barrier filter system. An example of baseline 50 degree pairs from subject Z3 is shown below demonstrating hidden parafoveal disturbances of the RPE with seemingly near normal fundus appearance and visual acuity.



Subject Z3 with 20/20-2 EDTRS acuity each eye: 50 degree retinal images above and 50 degree lipofuscin autofluorescent images.

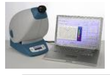
Skin carotenoids (Pharmanex®S2 Biophotonic Scanner) –

An LED based device that measures carotenoids in living tissue (human skin). This instrument is considered to be an indicator of the body's complete antioxidant network. The table shows the majority of patients (n=33) fell within the 2 lowest quintiles. However there appears to be little correlation between this measure of skin carotenoids and our measured foveal MP values (r = 0.11) .

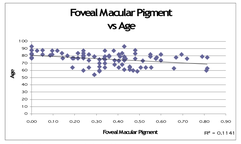
Table 2: Skin Carotenoids

Counts	<10,000	11,000-19,000	20,000-29,000	30,000-39,000	40,000-49,000	AVG	SD
Quantity	10	23	11	5	3	20,857	8,954

1 degree Foveal Macular Pigment Optical Density (MPOD)

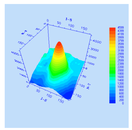


RIGHT EYES 0.35 (sd 0.2)
LEFT EYES 0.33 (sd 0.2)

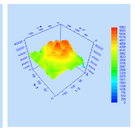


r = - 0.34 (inverse correlation with age)

Foveal 1 degree MPOD was evaluated with a modified Heterochromic Flicker Photometry clinical instrument **(i.e. QuantifEye® unit)** with an 8 degree eccentric fixation reference which, is assumed to be zero for all subjects. Replicate central readings were taken and averaged. The correlation coefficient for age vs. MP is r = - 0.34 indicating a trend for MP to be lower with age as reported by some groups. We also determined 14 degree MP distribution using an auto-fluorescence instrument developed and read by the laboratory of W. Gellermann, PhD, Depts of Physics/Ophthalmology, University of Utah.



Subject Z22 (MP =0.33)



Subject Z17 (MP = 0.21)

3D 14 degree Autofluorescent MP distribution maps of the population typically appear as illustrated on the left. However, a number of subjects have crown like distributions *(with a central depression)* as illustrated on the right.

CATARACT LENS OPACIFICATION CLASSIFICATION GRADE (LOCIII).

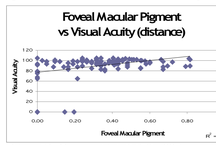
The confounding influence of lens opacification on visual function is assessed at ZVF Baseline and Final visit (1 year). The baseline data is presented below indicating a general low degree of opacification in our population and expected inverse correlation with MP.

LOCS III Opacification rating & correlation "r" with MP					
R eyes			L eyes		
Nuclear	Cortical	PSC	Nuclear	Cortical	PSC
2.25 sd 1.4	1.26 sd 0.9	0.87 sd 0.4	2.36 sd 1.4	1.26 sd 0.9	1.36 sd 0.4
r = - 0.07	r = - 0.08	r = - 0.07	r = - 0.08	r = - 0.07	r = - 0.26

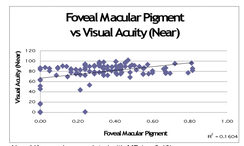
MACULAR FUNCTION VISUAL MEASUREMENTS: All testing is monocular with a single examiner (CT), single examination room and 5500K lighting. Patients are refracted for **best-corrected visual acuity** and evaluated with the **EDTRS chart at 3 meters** (M&S Technologies, Skokie, IL, Smart System ® II) by a single examiner (SR).

RIGHT EYES
93.5 (sd 15.1) – approx 20/25

LEFT EYES
90.6 (sd 18.2) – approx 20/30



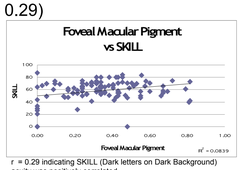
Distance EDTRS was correlated with MP (r = 0.37)



Near VA was also correlated with MP (r = 0.40)

Colenbrander Mixed Contrast Reading Card ® (10% Weber fraction) – a near reading card assesses visual function at low contrast. We also assessed the SKILL (Smith Ketterwell Low Luminance) test score for our subjects. Higher foveal MP values were associated with better low luminance SKILL scores (r = 0.29)

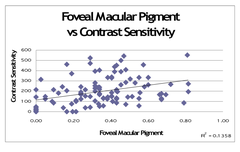
RIGHT EYES
86.7 (sd 19.0) High Contrast
74.1 (sd 18.2) Low Contrast
LEFT EYES
84.2 (sd 19.5) High Contrast
70.2 (sd 24.2) Low Contrast



r = 0.29 indicating SKILL (Dark letters on Dark Background) acuity was positively correlated.

Comprehensive DISTANCE Contrast Sensitivity – The Stereo Optical F.A.C.T. (Functional Vision Analyzer® Stereo Optical Co, Inc, Chicago, IL) CSF system is utilized at multiple spatial frequencies. The baseline global AUC (Area under the curve) was quite low in most cases despite impressive visual acuity. Note higher foveal MP values were associated with better global CSF values (r= 0.37) as reported previously in the LAST study.

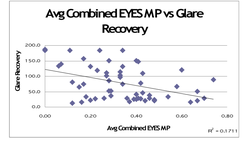
R EYES 205 (sd 129) - low
L EYES 189 (sd 136) - low



r = 0.37 is the correlation between MP and global CSF (area under the curve).

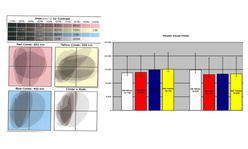
Photostress- Glare Recovery Japanese ophthalmologists use the KOWA AS-14B to assess night vision driving safety. It consists of a 30 second white field photo-stress stimulus / low contrast landolt C and timing circuitry. Our population data indicates delayed photo-stress recovery as reported in the LAST study.

R EYES
1st attempt 75.5 sec (sd 70.6)
2nd attempt 82.4 sec (sd 73)
L EYES
1st attempt 61.9 sec (sd 70.5)
2nd attempt 73.3 sec (sd 69.5)



Higher average eyes foveal MP was associated with better average eyes glare recovery. (r = - 0.41) as reported in the LAST study and by other groups.

Rush Ophthalmics – 3 wavelength / 5contrast SimulEyes® Kinetic Visual Field Test.



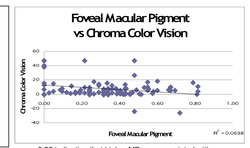
	OD White	OD Red	OD Blue	OD Yellow	OS White	OS Red	OS Blue	OS Yellow
100% Contrast	4,208.4	9,374.0	4,879.4	5,433.9	5,077.4	5,121.6	5,043.8	4,019.5
80% Contrast	5,701.5	5,468.4	5,498.4	5,499.5	3,751.5	3,751.5	4,820.4	4,044.8
60% Contrast	5,646.6	4,895.4	5,964.3	5,640.6	4,529.3	4,529.3	4,368.9	4,653.1
40% Contrast	6,301.9	5,705.2	6,483.4	5,899.0	4,709.4	4,709.4	4,993.4	5,080.9
20% Contrast	4,666.0	5,831.2	6,825.4	6,424.0	5,180.7	5,180.7	5,891.9	5,267.3
Total of each Contrast %	26,514	31,264	29,651	28,697	23,248.3	23,292.5	24,918.4	23,066.6
STDEV	850.2	6,252.8	5,930.2	5,739.4	4,649.7	4,658.5	4,983.7	4,613.1

Color Vision is measured with the Chroma ® Test: It measures threshold in the eye's ability to see short wavelength and long wavelength large (6.5 degree) stimuli. This is accomplished by reading different colored letters on a high resolution 32 bit color rate, high frequency computer monitor using proprietary software from ChromaTest®

Figure 1
The patient's view of two of the stimuli. In a test for ARM. These stills show the luminance noise. (squares) the size of 1 inch matches the optotype size.

TRITAN RIGHT EYES (6.5 deg)
6.58 SD (sd = 11.3) - abnormal
TRITAN LEFT EYES (6.5 deg)
8.27 SD (sd = 12.6) - abnormal

Note that any value above 2.5 sd is considered abnormal. Higher foveal MP was associated with better (lower) Chroma® thresholds (r = - 0.25). The confounding effect of lens opacification has not been factored in.



r = - 0.25 indicating that higher MP was associated with better Chroma ® thresholds.

DISCUSSION

A. Despite excellent EDTRS visual acuity, numerous visual function parameters are adversely affected in mild and moderate atrophic AMD. These include contrast sensitivity, low luminance vision, glare recovery and tritan color vision. Clinical Snellen acuity is irrelevant with respect to assessment of atrophic AMD in the exam room. This may explain, in part, the reason a physician may often under-estimate the impact of AMD associated visual disability.

B. Self described general health (score 65) and driving ability (score 72) are the most severely affected NEI VFQ25 factors affected in mild and moderate AMD within this AMD population. There is a weak correlation (r = 0.33) between foveal MP and the NEI VFQ (Visual Functional Questionnaire) global rating and driving subscale (r = 0.38), but not overall health.

C. There appears to be no correlation between Pharmanex® Biophotonic Skin Carotenoid levels and Foveal MP in this AMD population.

D. There is a weak inverse correlation between MP and age, and MP and % Body-Fat in this AMD population as reported by other groups.

E. There are weak positive correlations between MP and distance EDTRS VA (r = 0.37), near VA (r= 0.40), CSF (r = 0.37), SKILL low luminance acuity score (r = 0.29), and an inverse correlation with glare recovery (r = - 0.41) and large 6 degree Tritan color vision thresholds (r = - 0.25).

F. *On neuropsychological assessment, *data not shown, mean sample "Immediate memory" fell within the Low Average population range. This parameter was weakly correlated with average eye MP (r = 0.17).

G. *There was a similar correlation between sensory retinal blood flow in better vs. worse functioning eyes (r = 0.59) and R eyes vs. L eyes (r = 0.58) suggesting that sensory retinal blood flow (as opposed possibly to choroidal blood flow) is not a useful discriminating factor in mild and moderate AMD. *Blood flow data not shown.

ZVF STUDY OBJECTIVES: (Expected data 5-09)

To evaluate whether or not dietary supplementation with the carotenoid zeaxanthin alone raises macular pigment optic density (MPOD). Previous research has shown MPOD to mirror visual benefits for patients with age related atrophic macular degeneration (AMD) having visual symptoms (decreased visual acuity, contrast sensitivity, photostress glare recovery and NEI VFQ25 scores), but lower risk NEI / AREDS characteristics.

To evaluate whether supplemental 8 mg zeaxanthin has additional MPOD (and visual benefits) when added to approximately 10 mg lutein which has previously been found to be beneficial to patients with early and moderate AMD in LAST and other studies (i.e. LUXEA, CARMIS, LUNA & TOZAL).

Author Disclosure Information: S.P. Richer, Chrysantis, Inc, F; Kowa Co. JP, F; Stereo Optical, Inc, F; Pharmanex, Inc, F; ZeaVision, Inc, F; Heidelberg Engineering, F; Rush Ophthalmics, Inc, **W. Stiles**, None; **K. Graham**, None; **C. Thomas**, None; **L. Clouser**, None; **J. Nyland**, None; **P. Touzeau**, None; **J. Bekritsky**, None; **D. Richer**, None; **D. Park**, None.