RETINA INTERNATIONAL

Seeking A Cure For
Retinitis Pigmentosa (RP), Macular Degeneration, Usher Syndrome & Allied Retinal Dystrophies

Minutes of the 2015 Meeting of the Scientific and Medical Advisory Board of Retina International

Date: **Monday, 4th May, 2015**
Time: **1:00 - 2:30 p.m.**
Location: **Colorado Convention Center - Room 705/707**

A) Introduction

1) Greetings - Ms. C. Fasser, President, Retina International
2) Scientific Program Introduction – Drs. E. Zrenner and J. Hollyfield, co-chairmen, Scientific & Medical Advisory Board

B) Scientific Program

Retinitis Pigmentosa and Rare Diseases

1) PROGSTAR Program – Dr. Hendrick Scholl
2) The DRUGSFORD Project: Orphan Drug Status Obtained for the First Lead Compound Formulation - Dr. Francois Paquet-Durand
3) RD-Cure: Preparation for the ClinicalTrial in CNGA3-achromatopsia -Dr. Sttylianos Michalakis
4) Unoprostone Clinical Trial Update -Dr. Akira Murakami
5) LCA RPE65 Gene Therapy Clinical Trial Update – Dr. William Hauswirth
6) LCA RPE65 Gene Therapy Clinical Trial Update - Dr. Robin Ali
7) Optogenetics Update – Dr. Serge Picault
8) MERTK Trial Update – Dr. Nicola Ghazi

Macular Degeneration

9) Stem Cell Therapy for AMD – Dr. Conor Ramsden for Dr. Pete Coffey
10) IPS Cells: Clinical Trial for Macular Degeneration: An Update - Dr. Masayo Takahashi
11) RTH258 (ESBA1008), A Novel Anti-VEGF Antibody Fragment for AMD - Dr. Dominik Escher
12) Sustained Vision Loss in AMD: The CATT Study - Dr. Daniel Martin

13) Carotenoids in AMD: The CAREDS – Dr. Paul Bernstein
14) Genetic Susceptibility, Dietary Antioxidants and AMD – Dr. Carolyn Klaver

C) Retina International Announcements, New Business and Conclusions

1) New Business and Announcements – from the floor
2) Final Comments – Ms. C. Fasser

Attendees

Retina International Officials

President:	Ms. Christina Fasser
SMAB co-chairman:	Dr. Eberhart Zrenner
SMAB co-chariman:	Dr. Joe Hollyfield
SMAB secretary	Dr. Gerald Chader

Speakers

Ali Robin;Michalakis Stylianos; Bernstein Paul;Murkami Akira Escher Dominik; Paquet-Durand Francois; Ghazi Nicola; Picaud Serge; Hauswirth William; Ramsden Conor; Klaver Caroline; Scholl Hendrick; Martin Daniel; Takahashi Masayo;

Participants

Aguirre Gustavo
Andreasson, Sten
Badura, Franz
Boeni, Barbara
Carmichael, Trevor
Cremers, Frans
Cuenca, Nicolas
de la Rosa, Enrique
Dryja, Thaddeus
Flannery, John
Fletcher, Erica
Ghosh, Fredrik
Gonzales, Corinne
Grimm, Christian
Heon, Elise
Humphries, Marian
Humphries, Peter
Kellner, Ulrich
Kjellstrom, Sten
Koeneskoop, Robert
Kondo Mineo
Limb, G. Astrid
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Neiderhart, John
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Pinilla, Isabelle
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Preising, Markus
Prener Holtan, Josephine
Resende, Rosane
Sallum, Juliana
Sankila, Eva-Maria
Schorderet, Daniel
Shaberman, Ben
Simonelli, Francesca
Testa, Francesco
Tochitsky, Ivan
Tumminia, Santa
Ueffing, Marius
Vaklavic, Veronika
Vincent, Andrea
Vingolo, Enzo Maria
Weber, Bernhard
Wenzel, Andreas
Zilliox, Patricia

Meeting Abstracts

1) The ProgStar Program.

Dr. Hendrick Scholl

Sponsored by the Foundation Fighting Blindness, the ProgStar studies (A Natural History of the Progression of Stargardt Disease: Retrospective and Prospective Studies; ClinicalTrials.gov Identifier: NCT01977846; http://progstar.org/) are comprised of retrospective and prospective observational studies. The retrospective study includes clinical examination findings and images collected between 2008 (and earlier) and 2014 and progression will be retrospectively evaluated. The prospective study consists of a 24 month observational period from 2013/2014 for two years, with one visit every six months. The study population will include 250 STGD patients in the retrospective study and 250 patients in the prospective study recruited currently at 9 clinical centers across the U.S. and Europe. The enrollment of a large population of children and adults with STGD will assist in evaluating efficacy measures for future clinical trials. The outcomes of interest are measured via imaging (i.e., spectral-domain optical coherence tomography, fundus autofluorescence) and psychophysical testing (i.e., visual acuity, microperimetry). Images are evaluated by a central Reading Center at the Doheny Eye Institute, Los Angeles, California. The Data Coordinating Center is located within the Dana Center for Preventive Ophthalmology, Johns Hopkins University School of Medicine, Baltimore, Maryland. The objective of the ProgStar studies is to determine the progression of disease in a large population of children and adults over at least a two year period, with a variety of potential measures. The primary aim is to assess the yearly rate of progression of STGD using the growth or the development of atrophic lesions as measured by FAF imaging. Secondary aims are: (1) to assess the yearly rate of progression of STGD using Spectral domain optical coherence tomography (SD-OCT) to measure the rates of retinal thinning and the loss of photoreceptors; (2) to assess the yearly rate of loss of retinal sensitivity as measured by microperimetry; (3) to assess the yearly rate of BCVA changes; in the prospective study, measurements will be based on measurements the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol; (4) to correlate the presence and progression of morphological abnormalities in FAF and SD-OCT images with visual function as measured by MP and VA; (5) to perform exploratory analysis of factors associated with STGD progression, such as participant's use of vitamin A supplementation and mutations in the ABCA4 gene.

2) The DRUGSFORD Project: Orphan Drug Status Obtained for the First Lead Compound Formulation.

Dr. Francois Paquet-Durand

The EU-funded DRUGSFORD project aims to produce new drugs for the treatment of hereditary retinal degeneration (RD). To overcome the problem of genetic heterogeneity in RD, DRUGSFORD focuses on cGMP signalling as a therapeutic target and develops novel cGMP analogues as therapeutic agents. For efficient delivery across the blood-retinal-barrier, cGMP analogues are encapsulated into an innovative liposomal drug delivery vehicle so that they can get into the photoreceptor cells and exert their beneficial effect.

The DRUGSFORD consortium has two industrial and three academic partners. The company BIOLOG (Bremen, Germany) is the world leader in producing nucleotide analogues that can target and modify cGMP-signaling. BIOLOG´s compounds are encapsulated into a proprietary liposomal drug delivery vehicle developed by the company to-BBB (Leiden, The Netherlands). The novel compounds and their liposomal formulations are tested in a step-wise fashion in three different systems of increasing complexity:

1. Valeria Marigo (University of Modena, Italy) is testing DRUGSFORD compounds in photoreceptor-like cell cultures.
2. Positive hits are further tested in organotypic retinal explants cultures by Per Ekström (University of Lund, Sweden).
3. Compounds that pass the second step are tested in various RD animal models, *in vivo* by François Paquet-Durand (University of Tübingen, Germany).

At the current stage, the consortium has produced over 220 novel compounds, more than 150 of these were tested in cell-free assays, 25 compounds were tested in photoreceptor-like cell cultures, 11 were tested in retinal explants, and 4 were tested *in vivo* in the *rd1* mouse. One liposomal compound formulation – called LP-DF003 – resulted in a significant photoreceptor rescue in *rd1, rd2,* and *rd10* mice (with *cpfl1* mice and P23H rats still being investigated). Importantly, in at least 2 of these models (*rd2*, *rd10*), a morphological rescue also resulted a highly significant improvement of retinal function, as assessed in ERG recordings.

Consequently, the consortium selected LP-DF003 as the first lead to be developed for Phase I clinical testing. To this end, the consortium has recently obtained an orphan drug designation (ODD) for LP-DF003 from the European Medicines Agency (EMA; EU/3/15/1462). Although the further development of LP-DF003 was delayed by the bankruptcy of the industrial partner to-BBB, the consortium is currently negotiating with a potential new partner to forward the production of LP-DF003 according to GMP standards.

In summary, DRUGSFORD has identified cGMP signalling as a new common target for the treatment of RD, it has produced new compounds with unique and highly target specific properties, and it has adapted and developed a new liposomal drug delivery technology for efficient delivery to retinal photoreceptors. DRUGSFORD has obtained an ODD for its first lead compound formulation and aims to develop it further until the Phase I clinical stage.

3) RD Cure: preparation for the Clinical trial in CNGA3-Achromatopsia.

Dr. Stylianos Michalakis

Achromatopsia is an inherited, genetic disease caused by congenital loss of cone photoreceptor function and subsequent degeneration of cone photoreceptors. It is associated with strongly impaired daylight vision, photophobia, nystagmus and, of course, lack of color discrimination. Currently, 6 disease genes are known. However, the majority of patients carry mutations in the genes *CNGA3* or *CNGB3*, which encode the two subunits of the cyclic GMP-gated cation channel in cone photoreceptors.

In the past, we developed a curative treatment based on adeno-associated viral vector-mediated gene supplementation for CNGA3-linked Achromatopsia, also known as Achromatopsia type 2 (ACHM2). The successful proof-of-concept studies

in the CNGA3-deficient mouse model of Achromatopsia encouraged us to move the approach further to the clinics.

In 2012 we established the RD-CURE research consortium at the Universities of Tübingen and Munich and, in October 2012, we received funding from the Tistou and Charlotte Kerstan Foundation to initiate the translational studies.
Since then, we have generated and tested extensively a recombinant AAV8 vector that expresses human CNGA3 specifically in cone photoreceptors. This vector was used to manufacture GMP-grade toxicological and clinical batches at high quality and quantity. The vector was then successfully tested for transgene expression and biological activity in the CNGA3 knockout mouse model of Achromatopsia. Subsequently, we performed two GLP safety studies in non-human primates (*Cynomolgus* monkeys). The major study was a 13-week combined toxicology and biodistribution study with four study groups a total number of 22 animals. All animals received a single unilateral injection into the eye. One group received a subretinal injection of the highest foreseen clinical dose; a second group received a subretinal injection of a dose, which was one log unit higher than the highest foreseen clinical dose. A third group received vehicle only. The fourth so called "mis-dosing group" received an intravitreal injection of the 10-fold dose to mimic unintended complications during surgery. The analysis focused on toxicology and pharmacokinetics of the vector, but also included local and systemic immune response or functional tests like ERG. In addition to this extended study we performed a second interim study with necropsy at 4 weeks to investigate potential acute toxicological effects. Both studies have been successfully competed with no major adverse findings.
This year, we filed the final applications for a phase I/II clinical trial to our national regulatory authority (the Paul-Ehrlich-Institute, PEI) and the ethics committee of the Tübingen University Eye Hospital. The ethics committee just approved our study and we are awaiting the response of the German regulatory authority by the end of this month. Patient recruitment and pre-trial clinical assessment has been completed. Among 40 patients that have been examined, 9 patients have been selected to participate in the gene therapy trial.
The trial is planned as an exploratory, dose-escalation study with a "stackered design", three dosage groups and three patients in each group. The first patients will receive a single subretinal injection in one eye with the lowest vector dose. After positive evaluation of the outcome by the data monitoring committee, the next three patients will receive a half log unit higher dose. The final three patients will receive the high dose, which is one log unit higher then the low dose; again after we received the green light from the data monitoring committee, which consists of independent experts in the field. The observation time will be 12 months with a follow-up period of 4 years. The primary focus of the study is on safety, however it will also contain efficacy parameters as secondary endpoints. Upon approval we will initiate the clinical trial, which will hopefully be within 2015.

Discussion

Question by Dr. H. Scholl, Baltimore: *"What efficacy tests are foreseen in the trial?"*
Answer by Dr. S. Michalakis: *"The study protocol lists 14 tests as secondary endpoints for the assessment of efficacy, including visual acuity, contrast sensitivity, microperimetry, AO-LSO or ERG measurements."*

4) Unoprostone Clinical Trial Update.

Dr. Akira Murkami

I would like to report a short summary of Phase III trial of Unoprostone for RP in Japan, which had been initiated by Dr. Shuihi Yamamoto. He could not come to this meeting so I will take his place for the report. Unoprostone (IU) is used topically to treat glaucoma and has been reported to have neuro-protective effects on retinal neurons in vitro and in vivo. Topical IU was approved for clinical use to treat glaucoma and ocular hypertension in Japan in 1994. In a drug re-profiling strategy, it was thought that IU could be effective as a safe drug for patients with RP. As we had reported in previous SMAB meetings, to determine whether topical IU can improve visual function in RP patients, a randomized, double-masked, placebo controlled, phase II safety/efficacy trial had been conducted at six ophthalmological centers in Japan from 2008 to 2010. In that study, the group taking four eye-drops per day had a significantly improvement in the mean values of the central four points HFA (10-2). Based on the above results, a phase III trial had been planned, recruiting patients with a mean pre-treatment retinal sensitivity of the central four points of <30 dB through HFA (10-2) along with a placebo group. The phase III trial has been conducted with 0.15% IU of the four-drops/day dose, 52 week-randomized, double-masked, placebo controlled trial. The primary endpoint of the study was defined as the changes in the value of the mean retinal sensitivity at four central points through HFA (10-2). And after that, all cases were planned to be treated with IU for an additional 52 weeks. The trials were started in March 2013 and 199 cases were employed in the 52 week-randomized, double-masked, placebo controlled trail at 38 sites in Japan. No serious side effects have been reported and it is proceeding nicely. We confirmed the therapeutic effectiveness of UI in some areas of the present clinical study. However, the primary endpoint was not statistically significant compared to the placebo control. The company has decided to close the additional 52 week-trial study for safety in the view of objectivity of the data obtained. Now, data are being analyzed from various angles and we are examining the possibility of new drug applications. For example, one of the subclass analyses has shown that UI might be more effective in some stages of disease in the patients.

5) LCA RPE65 Gene Therapy Clinical Trial Update.

Dr. William Hauswirth

Retinal gene therapy for Leber Congenital Amaurosis, an autosomal recessive childhood blindness, has been widely considered to be safe and efficacious. Three years after therapy, visual improvement was maintained, but the rate of loss of photoreceptors in the treated retina was the same as that in the untreated retina. We now describe 4-6 year follow-up data from three treated patients, each of whom had significant gains in visual function upon treatment. Topographical maps of visual sensitivity in treated regions, nearly six years after treatment for two patients and four and a half years after treatment for the third, indicate progressively reduced areas of improved vision. However, at this late stage, visual sensitivity was still significantly better than baseline performances years earlier at treatment. Based on these data, a treatment staging strategy is proposed for extending vision benefit beyond the 4-6 year period.

6) LCA RPE65 Gene Therapy Clinical Trial Update.

Dr. Robin Ali

Researchers at UCL Institute of Ophthalmology, Moorfields Eye Hospital and the NIHR Biomedical Research Centre at Moorfields Eye Hospital and UCL Institute of Ophthalmology have recently completed a first-in-human trial of gene therapy for Leber Congenital Amaurosis. Children with this condition lack night vision and lose daylight vision. The results of the trial will be published in NEJM on 4 May. Professor James Bainbridge, lead clinician said, "this study confirms our preliminary findings (published in NEJM, 2008) that gene therapy can improve night vision, providing further evidence of benefit in inherited blindness".

Improvements in retinal sensitivity were evident, to varying extents, in six participants for up to 3 years, peaking at 6 to 12 months after treatment and then declining. No associated improvement in retinal function was detected by means of ERG. Three participants had intraocular inflammation, and two had clinically significant deterioration of visual acuity. The reduction in central retinal thickness varied among participants. In dogs, RPE65 gene therapy with the same vector at lower doses improved vision-guided behavior, but only higher doses resulted in improvements in retinal function that were detectable with the use of ERG.

In conclusion, gene therapy with rAAV2/2 RPE65 vector improved retinal sensitivity, albeit modestly and temporarily. Comparison with the results obtained in the dog model indicates that there is a species difference in the amount of RPE65 required to drive the visual cycle and that the demand for RPE65 in affected persons was not met to the extent required for a durable, robust effect.

Professor Ali commented, "our latest results provide confirmation of efficacy but the data, together with results of a parallel study in dogs, indicate that the demand for RPE65 is not fully met with the current generation of vectors. We have concluded that early intervention using a more potent vector, expressing higher levels of RPE65 is likely to provide greater benefit and protection against progressive degeneration". The group has now developed a new, more powerful gene therapy vector and is aiming to test this in a second clinical trial.

This summary is taken from comments from Dr. Ali and press releases from Dr. Ali's academic institutions.

7) Translation of Optogenetic Therapy: Preclinical Tests in Non-Human Primates.

Drs. Deniz Dalkara, Serge Picaud, José Sahel

Experiments in blind rodents have demonstrated the feasibility of restoring vision using different optogenetic proteins expressed in different cell types. For the translation of therapeutic strategy to human patients, we have investigated the possibility of transfecting retinal cells in living non-human primates (macaques). To prepare for clinical trials, we are developing goggles to activate the optogenetic proteins, which require high light intensities for their stimulation.

Expression of the modified Channelrhodopsin 2 (CatCh) protein was obtained in retinal ganglion cells by intravitreal injections with an AAV vector and a specific promoter. Functional efficacy was demonstrated by both multielectrode array recording and patch clamp recording of retinal ganglion cells in the foveal ring. Expression of Green Fluorescent Protein (GFP) indicated up to a third of retinal

ganglion cells were transfected but GFP expression was not required to achieve function. No major inflammatory reaction was observed in these preliminary studies. Finally, the first goggle prototype was generated to demonstrate the feasibility of such high intensity stimulations.
These preclinical results in non-human primates confirm the possibility to reactivate retinal neurons using an optogenetic strategy by targeting retinal ganglion cells with a specific promoter. This project was possible thanks to a grant from the Foundation Fighting Blindness (FFB). The recent attribution of an important grant from the French Government should speed up the process toward clinical trials.

8) MERTK Gene Therapy for Patients with MERTK-Related Retinitis Pigmentosa.

Dr. Nicola Ghazi

MERTK is an essential component of the signaling network that controls phagocytosis in retinal pigment epithelium (RPE), loss of which results in photoreceptor degeneration. Previous proof-of-concept studies have demonstrated the efficacy of gene therapy in treating RCS rats with MERTK deficiency. We also confirmed the efficacy of delivering human MERTK (hMERTK) using adeno-associated virus (AAV2) in mouse models of MERTK-related retinal dystrophy as well as the safety of this vector in rats and monkeys. Based on these preclinical data, we conducted a phase I open-label, dose-escalation trial involving six patients with MERTK-related retinitis pigmentosa (RP). Subretinal injection of rAAV2-VMD2-hMERTK was associated with acceptable ocular and systemic safety profiles based on 2-year follow up. Three patients have also displayed measurable improved visual acuity following treatment in the injected eye although the improvement was lost by 2 years in two of these patients. Therefore, gene therapy for MERTK-related RP using careful subretinal injection of rAAV2-VMD2-hMERTK is not associated with major side effects and may result in clinical improvement in a subset of patients.

9) Stem Cell Therapy for AMD.

Dr. Conor Ramsden on behalf of Professor Pete Coffey

Worldwide, there are more than 10 centres that have submitted protocols for the use of stem cell-derived therapies to treat retinal disease. On the leading edge of this wave is Ocata therapeutics, formerly Advanced Cell Technology who published their first results from two patients in 2012, one with end stage dry AMD and one with Stargardts macular dystrophy treated with a suspension of human embryonic stem cell (HESC)-derived RPE-like cells. In 2015, they published data from 9 patients with dry AMD and 9 with Stargardt's macular dystrophy. Elsewhere in the USA, Stem Cells Inc. have proposed a trial using human foetal brain cells that are purified and expanded and transplanted into patients with dry AMD. Janssen Pharmaceuticals are planning a trial using cells derived from human umbilical cord tissue to treat dry AMD. The London Project to Cure Blindness headed by Drs. Pete Coffey and Lyndon da Cruz achieved full clinical trial approval in 2013 to undertake a trial to implant HESC derived RPE-like cells cultivated on an artificial polyester membrane as a monolayer. Earlier this year, The California Project to Cure Blindness, headed by Drs. Mark Humayun and Denis Clegg, received full approval from the FDA to commence a

similar trial to implant HESC-derived RPE-like cells as a monolayer on a parylene membrane.
The trial in London is expected to commence recruiting imminently, initially 3 patients followed by a four month stop and, subsequently, 7 more patients in the following 12 months. The target patients are RPE or patients with wet AMD and worsening vision despite Lucentis treatment, and can thus be considered a treatment trial.
The trial in California is expected to begin recruiting this summer and the target is end stage dry AMD. The first cohort of 6 patients will have vision of 20/400 in the treatment eye and the second cohort of 6 patients with vision of 20/100 in the treatment eye.

10) iPS Cell-Derived RPE Transplantation for Age-Related Macular Degeneration.
Dr. Masayo Takahashi

We aim to develop a treatment that replaces damaged RPE with normal, young RPE made from patients' own iPS cells to rescue photoreceptors in the neural retina.
The first in-man application of iPS-derived cells started in September 2014 and targeted the retinal disease Age-Related Macular Degeneration (AMD). Six months after the surgery, the grafted iPS-RPE sheet is well spread and good in color that means no immune rejection occurs without immunosuppression. The patient's visual acuity is stable, compared to the past history of deterioration even with multiple anti-VEGF injections. The primary endpoint is safety, mainly with regards to tumor formation and immune rejection which will be checked after 1 year.
Since autologous transplantation is time consuming and the cost is high, it is necessary to prepare allogeneic transplantation to establish a standard treatment. RPE cells are suitable for allogeneic transplantation because they suppress the activation of T-cells and it is possible that the rejection is considerably suppressed by using the iPS cell with matched three loci of HLA.

11) RTH 258 (ESBA 1008): A Novel anti-VEGF Antibody Fragment for AMD.
Dr. Dominik Escher

RTH258 (formerly ESBA1008) is a humanized single-chain antibody fragment (scFv) that inhibits all VEGF-A isoforms and has a molecular weight of only 26 kD which compares to 48 kD for ranibizumab or 115 kD for aflibercept. Due to its high stability and solubility, it is possible to concentrate RTH258 to up to 120 mg/ml, allowing the administration of 6 mg in a single 50 µL intravitreal injection to patients. This enables the delivery of a much higher molar dose in the same volume as the current VEGF inhibitors in clinical use, potentially prolonging the effect of duration. Furthermore, the small size of RTH258 leads to a fast systemic clearance, potentially lowering the risk of systemic side effects.

The first evaluation of RTH258 in humans with neovascular AMD investigated the safety, tolerability and effects of treatment on ocular outcomes following a single intravitreal injection in 4 ascending doses compared to ranibizumab (NCT01304693). 194 patients were randomized to one of 5 groups. For RTH258, 11 patients received 0.5 mg, 31 received 3.0 mg, 47 received 4.5 mg and 44 received 6 mg; 61 patients received 0.5 mg ranibizumab. RTH258 4.5 mg and 6.0 mg were noninferior to ranibizumab for mean change from baseline to month 1 in best corrected visual acuity

(BCVA) and central subfield thickness (CSFT). Duration of effect was longer for patients receiving RTH258 4.5 mg and 6 mg, with median time to reversion to standard of care treatment being 30 days longer for RTH258 6.0 mg than for ranibizumab. Thus, RTH258 has the potential for a prolonged effect of duration, resulting in less frequent injections, potentially reducing the treatment burden for patients. Adverse events were observed at low and similar rates across treatment arms.

In a phase II study (NCT01796964), RTH258 was compared against aflibercept. A total of 89 patients diagnosed with neovascular AMD were treated in the double-masked, multicenter, two-arm study. Eligible patients were randomized to receive either 6mg RTH258 or 2mg aflibercept. Treatment started with 3 monthly loading doses for both RTH258 and aflibercept. Following the loading phase, treatment was reduced to bi-monthly for both RTH258 and aflibercept up to week 32. Subsequently, RTH258 was reduced to treatment every 3 months and aflibercept was continued on a bi-monthly interval up to week 56. The primary objective of the study was change from baseline in visual acuity at week 12. Secondary objectives included change from baseline in visual acuity at week 16 and up to week 56 as well as change from baseline in CSFT by visit. The phase II study met its primary endpoint, demonstrating promising visual acuity gains that were non-inferior to aflibercept, with numerically greater reduction and rapid improvement in abnormal retinal fluid observed in RTH258-treated patients. Patients treated every three months with RTH258 experienced a prolonged duration of effect, potentially leading to a reduced treatment burden. Both RTH258 and aflibercept were well tolerated and no new safety signal was reported during the study.

With these positive results, Alcon has initiated the phase III clinical program to evaluate the efficacy and safety of RTH258 versus aflibercept in patients with neovascular AMD. Alcon expects to enroll approximately 1,700 patients in more than 50 countries worldwide. The primary objective of the first phase III study is to compare the efficacy of RTH258 3mg and 6mg versus aflibercept 2mg, with the mean change in BCVA from baseline to week 48 as the primary endpoint. The second phase III program will also compare the efficacy of RTH258 versus aflibercept and is expected to commence later this year. Patients participating in the phase III studies will be dosed every three months with RTH258, while a bi-monthly dosing regimen will be followed for those patients considered unsuitable for a quarterly dosing schedule due to disease activity. Aflibercept will be dosed according to its approved label.

12) Sustained Vision Loss in AMD: The CATT Study (Comparison of Age-Related Macular Degeneration Treatments Trials).

Dr. Daniel Martin and the CATT Research group

Although anti–vascular endothelial growth factor treatment of neovascular age-related macular degeneration (AMD) results in improved vision overall, loss of substantial vision can occur. Understanding the processes that lead to loss of vision may lead to preventive strategies. The objective of this study is to determine the incidence, characteristics, causes, and baseline predictors of sustained visual acuity loss after 2 years of treatment with ranibizumab or bevacizumab for neovascular AMD.

This is a cohort study within a randomized clinical trial of participants in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT).

Participants were randomly assigned to treatment with ranibizumab or bevacizumab and to 2 years of monthly or as needed injections or monthly injections for 1 year and as needed injections the following year.
The main outcome and measure was sustained visual acuity loss, defined as loss of 15 or more letters from baseline at weeks 88 and 104. Among 1030 participants, 61 eyes (5.9%) developed sustained visual acuity loss in 2 years. Within this group, visual acuity decreased gradually over time, with a mean decrease of 2, 19, and 33 letters from baseline at 4 weeks, 1 year, and 2 years, respectively. At 2 years, eyes with sustained visual acuity loss had more scarring (60.0% vs 41.4%, P = .007), more geographic atrophy (GA) (31.6% vs 20.7%, P = .004), larger lesions (16 vs 8 mm2, P < .001), and higher proportions of intraretinal fluid (82.5% vs 51.0%, P < .001), subretinal hyperreflective material (84.5% vs 44.2%, P < .001), retinal thinning (43.3% vs 23.0%, P < .001), and thickening (20.0% vs 12.1%, P < .001). Likely causes of sustained visual acuity loss included foveal scarring (44.3%), pigmentary abnormalities (27.9%), and foveal GA (11.5%). Baseline factors independently associated with a higher incidence of sustained visual acuity loss were the presence of nonfoveal GA (odds ratio [OR], 2.86;95%CI,1.35-6.08; P = .006), larger area of choroidal neovascularization (OR for a >4-disc area vs ≤1-disc area, 3.91; 95% CI,1.70-9.03; P=.007), and bevacizumab treatment (OR, 1.83;95%CI,1.07-3.14; P = .03).
In conclusion, sustained visual acuity loss was relatively rare in CATT. The development of foveal scar, pigmentary abnormalities, or GA contributed to most of the sustained visual acuity loss. Risk was 3% higher among eyes treated with bevacizumab. Treatment that targeted the prevention of scarring or GA may improve vision outcomes.

13) Lutein, Zeaxanthin, and *meso*-Zeaxanthin: The Basic and Clinical Science Underlying Carotenoid-based Nutritional Interventions Against Ocular Disease.

Dr. Paul S. Bernstein

The human macula uniquely concentrates three carotenoids: lutein, zeaxanthin, and meso-zeaxanthin. Lutein and zeaxanthin must be obtained from dietary sources such as green leafy vegetables and orange and yellow fruits and vegetables, while *meso*-zeaxanthin is rarely found in diet and is believed to be formed at the macula by metabolic transformations of ingested carotenoids. Epidemiological studies and large-scale clinical trials such as AREDS2 have brought attention to the potential ocular health and functional benefits of these three xanthophyll carotenoids consumed through the diet or supplements, but the basic science and clinical research underlying recommendations for nutritional interventions against age-related macular degeneration and other eye diseases are underappreciated by clinicians and vision researchers alike. In this talk, I will first examine the chemistry, biophysics, and physiology of these yellow pigments that are specifically concentrated in the *macula lutea* through the means of high affinity binding proteins and specialized transport and metabolic proteins where they play important roles as short-wavelength (blue) light-absorbers and localized, efficient antioxidants in a region at high risk for light-induced oxidative stress. There is clinical evidence supporting functional benefits

of these carotenoids in normal eyes and for their potential protective actions against ocular disease from infancy to old age.

14) Genetic Risk and Diet in Age-Related Macular Degeneration

Dr.Caroline Klaver, Erasmus MC, Rotterdam, The Netherlands

Supplements with high dose antioxidants have been shown to protect against progression of age-related macular degeneration (AMD). Nutrients in diet (lutein/zeaxanthin, zinc, omega-3) can also lower the risk, especially when intake is consistently high during many years. Whether dietary intake of antioxidants is effective in lowering a high genetic risk is of interest to patients and clinicians, as it can be an important lifestyle tool to counteract the development of AMD in those with high susceptibility. My group has investigated this relationship in the population-based Rotterdam Study in various time periods.

The first investigation (2011): we followed up persons without any Early or Late AMD (n=2167, age 55+ yrs) for 8 years and found that carriers of the CHF and ARMS2 risk alleles could lower their genetic risk by 35-50% when they are in the highest tertiles of dietary intake of zinc, beta-carotene, lutein/zeaxanthin and omega-3.

The second investigation (2014): we pooled our data with the Australian population-based Blue Mountain Eye Study and now evaluated development of AMD in 4632 persons during 15 years of follow up. For those at high genetic risk (based on carriership of the CFH and ARMS2 genes), we found the strongest risk reduction in those with high intakes of lutein/zeaxanthin (risk reduction 20%) and weekly intake of fish (risk reduction 40%).

The third investigation (2015) concerned the question: ‘what diet should one follow to lower the risk of AMD?’ To make the advice as simple as possible, we focused on the current advice of the National Health Council: 200 gr vegetables/day, 2 pieces of fruits/day, and 2x fish/week. We followed up 4797 participants aged 55+ yrs of the RS I up to 20 years and found that only 30% of the participants consumed the advised portion of vegetables, 54% consumed 2 portions of fruit/day, and 13% consumed 2x fatty fish per week. The combination of these 3 food groups was consumed by only 3.5% of the entire population. Of the individual food groups, intake of fatty fish (2x/week) had the most prominent effect on incident Early or Late AMD (HR: 0.74 [95%CI 0.59-0.94]). Intake of the advised combination of vegetables, fruits and fish led to a 44% risk reduction (HR 0.56, 95% 0.35-0.89, adjusted for age and sex).

Conclusion: All persons gain from eating a healthy diet with sufficient intake of anti-oxidants, but diet can particularly counteract a high genetic risk of AMD. Intake should be consistent during a long period. A diet beneficial for AMD is not complicated: follow the Health Council advice: 200 gr vegetables/day, 2x fruits/day, and 2x fatty fish/week.

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Note: In pooled data analyses, we found significant interaction between AMD genetic risk status and LZ intake (P=0.0009) but nonsignificant interactions between genetic risk status and weekly fish consumption (P=0.05) for risk of any AMD. Among participants with high genetic risk, the highest intake tertile of LZ was associated with a >20% reduced risk of early AMD, and weekly consumption of fish was associated with a 40% reduced risk of late AMD. No similar association was evident among participants with low genetic risk. No interaction was detected between β-carotene or vitamin C and genetic risk status.

RI Announcements, New Business and Conclusions
Announcements - none
Final Comments – Ms. Fasser thanked all speakers for their excellent presentations and wished everyone would have a very successful ARVO meeting.