RETINA INTERNATIONAL

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

Minutes of the 2019 Meeting of the Scientific and Medical Advisory Board of Retina International

Date **Monday, 29 April, 2019**
Time **1:15 - 2:45 p.m.**
Location **Vancouver BC Convention Center - Room East 18**

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A) Introduction

1. ***Greetings - Ms. C. Fasser, President, Retina International***

2. ***Scientific Program Introduction – Drs. Eberhart Zrenner and Joe Hollyfield, co-chairmen, Scientific & Medical Advisory Board***

B) Scientific Program

Multifactorial Retinal Diseases (e.g., AMD, Geographic Atrophy)

1) Clinical Trial for Geographic Atrophy using APL-2, a Complement Inhibitor.
Dr. Ramiro Ribeiro, Apellis Pharmaceuticals, Cambridge, MA, USA

Apellis is a company focused on the complement system; in particular, the inhibition of complement C3. The lead candidate drug, APL-2, is being investigated in C3-mediated conditions such as paroxysmal nocturnal hemoglobinuria and geographic atrophy (GA).

The Filly phase 2 trial was a 246-patient multicenter, randomized, single-masked, sham-controlled study to evaluate the safety, tolerability and efficacy of APL-2 in subjects with geographic atrophy associated with age-related macular degeneration (AMD). APL-2 was administered either monthly or every other month via intravitreal injection for 12 months followed by six months of safety monitoring without medication. The primary endpoint was the growth of GA lesions measured by fundus autofluorescence at different time points. Monthly administration of APL-2 showed a 29% reduction (p=0.008) in the rate of GA lesion growth compared to sham. With the every-other-month administration, a 20% (p=0.067) reduction was observed. A more pronounced effect was seen between month 6 and month 12. During the 6 months of off-drug treatment, the growth rate between groups was similar. The most frequently reported adverse events were associated with the injection procedure. Subjects in the APL-2 arm were at higher risk of conversion to neovascular AMD.

Based on the Phase 2 results, Apellis initiated 2 global Phase 3 studies in 2018. In these studies, subjects will be randomized to either monthly APL-2, every other month APL-2 or sham and followed for 2 years. The primary endpoint for the study will be the change in GA lesion at month 12 compared to baseline measured by autofluorescence. Results are expected by Q1 2021.

2) Gene Therapy for Geographic Atrophy
Dr. Robert MacLaren, University of Oxford, Oxford, UK

The first gene therapy clinical trial for dry AMD targeting retinal pigment epithelium with an AAV vector encoding a complement pathway regulator took place in Oxford on 17 January this year. Further patients have since been recruited and the trial is likely to be expanded internationally in the near future. The trial is sponsored by Gyroscope Therapeutics, a Cambridge University spin out company based in Stevenage. Some of the preclinical vector development work was carried out in the Nuffield Laboratory of Ophthalmology at the University of Oxford.

3) LEAD Trial: Nanosecond Laser Treatment for Intermediate AMD.

Dr. Erica Fletcher, The University of Melbourne, Melbourne Australia

Drusen are an important early feature of AMD, whose size is predictive of the risk of progression. Studies in the 1980s considered whether conventional continuous wave laser therapy that resolved drusen also reduced progression of AMD. However, some studies reported acceleration of disease, and thus, laser treatment was largely abandoned as a tool for reducing progression of AMD.

The nanosecond laser is a recently developed laser that is quite unlike its continuous wave predecessors. It is a 532nm pulsed laser, that selectively targets the retinal pigment epithelium (RPE) with single 3ns pulses. Importantly, it delivers a fraction of the energy of a thermal laser and has been shown to be safe in preclinical studies.

The **L**aser intervention in **E**arly stages of **A**ge-Related Macular **D**egeneration (LEAD) trial was a multicenter clinical trial that evaluated whether nanosecond laser treatment of patients with intermediate AMD could reduce progression to advanced disease (either signs of choroidal neovascularization, or atrophy. In total, 292 participants across five sites in Australia, and one in Northern Ireland were enrolled and treated with nanosecond laser (n=147) or sham (n=145) every 6 months for 36 months. Participants enrolled were those with intermediate AMD (i.e. large (>125um) drusen in both eyes) who had been carefully screened by OCT to be free of any sign of atrophy. Every 6 months, patients received 12 laser or sham laser spots around the macula in a manner that was not targeted to the drusen directly. Advancing disease was defined as the presence of any sign of atrophy on OCT, GA or CNV.

The main (primary) outcome of the LEAD trial, that nanosecond laser reduced progression of AMD was not achieved. Forty-five participants developed late AMD including 20 in the laser group and 25 in the sham group. However, an important observation was made that suggested that not all patients responded in the same way to the laser treatment. Using a post hoc analysis, patients with conventional (large) drusen showed a 4-fold reduction in progression, whereas those with reticular pseudo drusen (RPD) potentially showed an acceleration (worsening) in disease.

The outcomes of the LEAD trial are important for several reasons. First, it was the first clinical trial that used OCT-defined atrophy as a way to demonstrate advancement of disease. Secondly, the LEAD trial showed that those with RPD may respond in a different way to therapy to those with conventional drusen. Finally, the results of this trial provide valuable information about laser treatment as a means for reducing progression. Importantly, progression of AMD when all participants are considered together, was not reduced. Follow-up studies are required to validate the LEAD results and to evaluate how laser treatment effects disease progression in those with different forms of drusen. If the reductions in progression in those with conventional drusen are replicated, it would represent a major advance in how we manage and treat those with AMD.

4) Epidemiology of AMD and Visual Impairment in Denmark.

Dr. Michael Larsen. University of Copenhagen, Copenhagen, Denmark

The purpose of this study was to determine the incidence rates of legal blindness from age-related macular degeneration (AMD) and other causes in Denmark from 2010 to 2016 in the age group at risk of AMD – age 50 years or older. This is a population-based observational registry study using the membership registry of the Danish Association of the Blind, the primary admission criterion of which is best-corrected visual acuity of 0,1 (20/200) or lower in a person's better-seeing eye. Incident cases of legal blindness from the population of

citizens aged over 50 years with free access to a single-payer public health care system were used. The main outcome measure was the change in incidence rate of legal blindness from AMD from 2010 to 2016.

We found that the incidence rate of legal blindness attributable to AMD in citizens 50 years of age or older decreased from 25.7 cases per year per 100,000 persons in 2010 to 15.9 cases per year per 100,000 persons in 2016. This corresponds to a reduction of 38% over the period of 6 years (p less than 0.01 adjusted for age). The incidence of legal blindness from causes other than AMD was 10.6 cases per year per 100,000 persons and 9.6 cases per year per 100,000 in 2016 (p less than 0.05).

We conclude that legal blindness from AMD continues its 50% decline in the previous decade to decrease by an additional 20% of the year 2000 baseline rate from 2010 to 2016. The observation supports the idea that the efforts made to prevent blindness from AMD have been effective. A cost-effectiveness analysis was not included in this study and no information was available about the incidence of visual impairment milder than legal blindness. The stagnation in the rate of new cases of blindness from causes other than AMD should prompt further analysis.

5) Phase 3 Studies of Brolucizumab versus Afibercept in nAMD – an update. Dr. Glenn Jaffe

Withdrawn, ARVO abstracts available

6) Research-Based Free Sequencing of Genes Associated with Rare Inherited Eye Diseases.
Dr. Frans Cremers, University of Nijmegen, Nijmegen, The Netherlands

At the ERN-EYE meeting in Florence on October 12, 2018, research groups from across Europe volunteered to perform sequence analyses to identify the underlying mutations for one or more inherited eye disease(s). This initiative is important as many genetic centers cannot afford costly Sanger sequencing or next generation sequencing-based gene-panel sequencing. Almost all retinal disease-associated genes are covered including ABCA4 for Stargardt disease and CRD as well as USH2A in Nijmegen but we are still searching for labs that can offer free sequencing for autosomal dominant and/or recessive RP.

This genotyping can only be done in a research setting and diagnostic validation for clinical use, e.g., via Sanger sequencing of the identical variant(s) in the proband and/or family members should be done in a certified diagnostic laboratory afterwards. The research groups involved will benefit from the sequencing as they can study novel causes or mechanisms of disease. The terms of collaboration will be set by the sending party and the center of expertise. Each group has its own conditions for a collaboration. Written informed consent for the probands is always the responsibility of the physician involved. If there are any problems (e.g. regarding eligibility, turn-around times, etc.) an email can be sent to freeseq@radboudumc.nl.

This brochure can also be found at the Retina International website:
http://www.retina-international.org/free-research-based-sequence-analysis-of-genes-associated-with-rare-inherited-eye-diseases-in-centers-of-expertise/

Phenotype – Genes that are tested (City, Research leader)

✓ Achromatopsia – *CNGA3, CNGB3* etc. (Tuebingen, S. Kohl)

- ✓ Bardet-Biedl and Alström syndromes (*BBS1-BBS22* and *ALMS1*) (Strasbourg, J. Muller)
- ✓ Blue-cone monochromacy-X-linked - *OPN1LW/OPN1MW* (Tuebingen, S. Kohl)
- ✓ Congenital stationary night blindness – 12 genes (Paris, C. Zeitz)
- ✓ Cornea plana – *KERA* (Prague, P. Liskova)
- ✓ Fuchs endothelial corneal dystrophy - *TCF4* repeats (CTG18.1) (London, A. Davidson)
- ✓ Leber congenital amaurosis / early-onset retinal dystrophy; also syndromic with early onset retinal dystrophy – 70 genes (Paris, J-M. Rozet)
- ✓ North Carolina macular dystrophy – *PRDM13 IRX1* regions (Ghent, E. De Baere)
- ✓ Posterior polymorphous corneal dystrophy – *OVOL2* & *GRHL2* promoters (Prague, P. Liskova)
- ✓ Retinitis pigmentosa (sporadic or autosomal recessive) with one causal variant in *USH2A* after WES or Sanger sequencing of all *USH2A* exons (Nijmegen, S. Roosing)
- ✓ Retinitis pigmentosa (sporadic or autosomal recessive) with one causal variant in *USH2A* after WES or targeted sequencing of all *USH2A* exons (Ghent, E. De Baere)
- ✓ Stargardt disease & ar cone-rod dystrophy- *ABCA4* (Nijmegen, F. Cremers)
- ✓ Stargardt disease with one causal variant in *ABCA4* (Ghent, E. De Baere)
- ✓ Usher syndrome with one causal variant in *USH2A* (Nijmegen, H. Kremer)
- ✓ Usher syndrome type 2 (Nijmegen, H. Kremer)
- ✓ X-linked retinitis pigmentosa – *RPGR ORF15* (Paris; C. Zeitz & I. Audo)

7) Stagardt Disease ALK-001 Phase 2 Clinical Trial: 12 Month Interim Data. Dr. Hendrik Scholl, Johns Hopkins Hospital, Baltimore, MD, USA

STGD is a rare monogenic disease caused by ABCA4 gene defects. Despite being rare, STGD is the third most common monogenic recessive disease, more prevalent than cystic fibrosis but less prevalent than sickle cell disease. There are approximately 100,000 patients - US +EU. There is no approved treatment.

Patients with Stargardt lose central vision. ABCA4 defects disrupt transport of vitamin A through the photoreceptor layers causing accelerated formation of vitamin A dimers. Vitamin A dimers are toxic to the retina and are implicated in the pathology of Stargardt and AMD. Preventing vitamin A dimer formation may prevent the development or progression of Stargardt. Drugs that interact with the visual cycle have been tested in Geographic Atrophy. However,
because the eye relies on an uninterrupted supply and flow of vitamin A, these drugs result in side effects and potential long-term retinal toxicity.

• The research I have been involved with for 9 years deals with the development of ALK-001. ALK-001 is a chemically-modified vitamin A, where 3 hydrogen atoms have been replaced with 3 deuterium atoms. Deuterium is a heavy, non-radioactive isotope of hydrogen. By replacing hydrogen by deuterium, the rate of formation of vitamin A dimers is slowed by 4 to 5 times. ALK-001 is delivered orally as a once a day pill. During this first Phase 2 clinical trial, we attempted to evaluate the long-term safety of ALK-001 and estimate the time it takes to replace and the extent of vitamin A replacement in plasma. In addition, we collected ocular outcomes to measure the effect size on the progression of Stargardt disease.

In this first Phase 2, named “TEASE”, we have enrolled 50 participants at 7 US-based clinical sites. Inclusion criteria included patients who have confirmed Stargardt and a well

delineated area of atrophy. This area of atrophy has been accepted by the FDA as an approvable endpoint, so it was natural to start the program with this patient population. Patients ranged between 18 and 60 years old, with an approximate disease duration of ~10
years and a visual acuity of ~20/80. This is a relatively small study, so it is powered for safety. The efficacy outcome measures include growth rate of atrophic lesions, visual acuity, reading speed and retinal sensitivity.

After 12 months of treatment, the study drug showed excellent tolerability with minor side effects as expected with vitamin A. No patient showed elevated liver enzymes or clinically significant changes in a comprehensive metabolic panel. Importantly, there was no report of night blindness or delayed dark adaptation as would be expected if ALK-001 did not behave identically to vitamin A. ALK-001 was able to replace 80% of vitamin A with deuterated vitamin A after only 4 weeks of treatment, and over 90% after 6 months. There was no increase in the total amount of vitamin A in plasma. No dietary restriction was required, except the obvious avoidance of liver and vitamin A
supplements. The last patient‘s last visit will take place this year, and I hope to be able to present final safety data and data on effect size next year.

In conclusion, ALK-001 is a clinically friendly tool to evaluate the contribution of vitamin A dimer in retinal degeneration. We hope that the study will show a positive effect on atrophic lesions. Data to date indicate that the measurement of atrophic lesions is a feasible endpoint in Stargardt disease. Safety and pharmacokinetic data have supported the start of a new study called “TEASE-2” in patients with an earlier stage phenotype, as well as “SAGA”, the study of ALK-001 in Geographic Atrophy.

8) Trials for Lipofuscin Removal in Stargardt Disease with Soraprazan. Dr. Andrew Lotery, University of Southampton, Southampton, UK

Soraprazan is a drug capable of stopping progression of atrophic macular degeneration associated with the accumulation of lipofuscin in cells of the retinal pigment epithelium (RPE). Front runner indication is that Stargardt’s disease (STGD) is an orphan indication with about 100.000 patients in the US and EU. The EMA and the FDA have granted orphan medicinal product designation for Soraprazan for the treatment of STGD. A private/academic consortium of five academic clinics and an industry CRO have received EUR 6m for a phase 2 POC clinical study with Soraprazan in STGD.

Soraprazan is a small molecule capable of removing lipofuscin from RPE cells. It reduces existing levels of lipofuscin in the RPE instead of merely slowing down further deposits. The removal of lipofuscin from living cells is a paradigm-breaking discovery. This effect has hitherto been thought to be impossible. It has now been demonstrated in primates, in cultured primary human RPE cells, and in STGD knock-out mouse models.

The Phase 2 study has now been given ethical approval to start in Southampton, England in Prof Lotery’s clinics with other sites in the Netherlands, Germany and Italy to start soon. Prof Carel Hoyng is the overall Chief investigator for the study.

After the meeting, Dr. Lotery sent us the following addendum in reply to some comments after his talk on Soraprazan suggesting the drug is toxic to the retina:

In reaction to these comments, the Consortium of investigators doing the clinical trial had a diligent review of all available safety information by their experts for non-clinical and

clinical safety. Soraprazan is a re-purposed drug that was ready for phase III for the indication gastro-esophagal reflux disease (GERD). The data available for the assessment of the safety of the drug is extensive. As a result of the safety review, no reason was identified to change the protocol, amend the clinical trial submissions or even withdraw the trial. Soraprazan (Remofuscin) has proven to be safe in the eye in various non-clinical toxicity models with sufficient threshold to the dose used in humans.

This is not only the Consortium's own perception. It is also the view of four competent authorities in Europe in countries with planned trial centers of the Remofuscin study. None of the reviewing regulatory authorities were concerned with regard to protocol, non-clinical safety or clinical safety in their responses to our submission. Further, in preparation of the trial, the Consortium asked for scientific advice from a fifth European competent authority which likewise endorsed the non-clinical and clinical safety package.

With respect to Quantitative Autofluorescence (qAF), this remains the only reliable method to measure changes in retinal autofluorescence (which correlates with lipofuscin content). It is achieved using the Heidelberg Spectralis after minor mechanical modifications to the camera head, new firmware to the camera, and to the acquisition and viewing software. The laser power used is slightly reduced compared to the normal AF technique and spread over a larger area.

It has been hypothesised that the “light adaptation” process of the photoreceptors during qAF measurements may be detrimental to the retina, especially in pathological situations. This requires approximately 30 seconds with the 488-nm light of the Spectralis to minimize pigment absorption. This light is quite bright (5.1 log photopic Trolands) and causes discomfort for some patients (even when gradually implemented). The overall duration for light adaptation and imaging for each eye is typically less than 2 minutes. qAF has been safely used in several studies (also including STDG patients) to date with no reported adverse effects. For comparison, the same equipment when used for fluorescence angiography requires a total exposure time of 5 – 10 minutes, and for routine AF 1 – 2 minutes. The irradiance of AF is 330 lW/cm2 (488 nm, 308 field; 260 lW beam power), which is below the permissible exposure recommended by the ANSI standards for durations of up to 8 hours (permissible levels are approximately 10 times lower than damage threshold).

This said, unexpected toxicity is a possibility in any clinical trial. Therefore, safety is always subject of scrutiny. Hence, the protocol of the clinical trial involves a number of safety measures that assure the sensitive and early detection of toxicity to the retina if encountered during the treatment period. Adverse events are subject to immediate reaction by a Data Safety Monitoring Board. In the event that toxicity is observed, measures include to stop treatment or ultimately stop the trial. Unfortunately, the non-clinical and clinical data on safety the Consortium uses for the submission is for the largest part licensed by Katairo GmbH from Takeda under obligations to maintain confidentiality. Therefore, details can be and are shared within the consortium under obligations to maintain confidentiality. But details cannot be shared with the public.

I hope this will reassure attendees at the meeting regarding the trial.

9) jCyte I/IIa Clinical Trial for RP Using Stem Cell Technology. Dr. Baruch Kuppermann, University of California, Irvine, Irvine, CA, USA

RP is an incurable blinding disease caused by death of first rod, then cone, photoreceptors in the retina. Preclinical studies have demonstrated that transplantation of retinal

progenitor cells into the eye can significantly slow photoreceptor loss. We assessed the safety and activity of human retinal progenitor cells (hRPC) in a first-in-human clinical study.

A phase 1/2a multicenter open-label study (NCT02320812) evaluated 28 patients (ages 18 -73 years) with RP in two vision cohorts: best-corrected visual acuity (BCVA) in the treated eye was between 20/200 and “hand motions” in the first cohort and 20/63-20/200 in the second. Patients received a single intravitreal injection of 0.5, 1.0, 2.0 or 3.0 million hRPC (jCell; jCyte, Newport Beach, CA). Safety and efficacy were evaluated at scheduled intervals through 12 months post-treatment. Safety was demonstrated at each dose level in cohort 1 subjects before proceeding to a higher dose level in the same cohort and before cohort 2 subjects could be enrolled at the same dose level.

Treatment-related adverse events were reported in 21 subjects (75.0%) and were mostly mild to moderate and transient. Although the study was not powered or designed to assess efficacy, BCVA and other parameters were monitored over 12 months. Vision of hand motions or counting fingers were scored as zero letters correct for purposes of analysis. Mean change in BCVA from pre-treatment to month 12 (treated eye minus untreated eye) was 3.64 letters for all study subjects, 1.38 letters for the 0.5M dose group, 1.00 letter for the 1.0M dose group, 4.83 letters for the 2.0M dose group and 9.00 letters for 3.0M hRPC. When subjects without measurable BCVA at baseline (n = 8) were excluded, the difference in mean change in BCVA (treated eye - untreated eye) at 12 months was 1.83 letters for the 0.5M dose group, 0.17 letters for the 1.0M dose group, 7.50 letters for the 2.0M dose group and 11.25 letters for 3.0M hRPC.

We found that intravitreal injection of hRPC was safe and well-tolerated at doses up to 3 million cells. The change in BCVA between treated and untreated eyes was positive at all dose levels, with suggestion of a dose response at the higher dose levels. A phase 2b masked, controlled study designed to confirm efficacy using BCVA and other potentially more sensitive endpoints is currently ongoing.

10) GenSight Use of Optogenetics/Gene Therapy in Retinal Degeneration. Dr. Serge Picaud, INSERM, Paris, France

Gensight Biologics (Paris. France) has started clinical trials in Europe for optogenetic therapy in blind patients affected by retinitis pigmentosa to restore vision. The viral vector for the therapy is an AAV2-7m8 capsid and it carries the genetic code for the microbial opsin, ChrimsonR-tdTomato. This vector was previously shown to allow expression of ChrimsonR-td Tomato in retinal ganglion cells in, giving, non-human primagtes. This opsin expression had rendered retinal ganglion cells directly sensitive to light as observed when blocking synaptic transmission. Three patients have now been injected with the lowest dose of the vector, generating no major inflammation. A higher dose of viral vector will soon be injected in other patients. Future investigations will measure how ChrimsonR-tdTomato expression can restore light perception in these blind patients.

11) ProQR Use of a New Drug for Treatment of LCA Type 10 (CEP290). Dr. Artur Cideciyan, University of Pennsylvania, Philadelphia, PA, USA

Dr. Cideciyan provided an update on the Phase I/II trial by ProQR. CEP290 is expressed at the connecting cilium of rods and cones. The retinal phenotype of patients with *CEP290* mutations often involves an elliptical macular region of retained cone photoreceptors lacking function. One of the common alleles is an intronic mutation between exons 26 and 27 that creates a splicing defect. An antisense oligonucleotide (ASO) was designed by

ProQR to restore correct splicing and increase the expression of wildtype CEP290 protein. A Phase I/II clinical trial to evaluate the safety and tolerability (ClinicalTrials.gov number: NCT03140969) started in November of 2017 at three centers: Iowa and Philadelphia, USA, and Ghent, Belgium. Substantial improvement in vision in one patient prompted the decision to perform interim analyses of all data. Ten subjects were injected at least once and up to four times; eight subjects had at least 3 months and four subjects had at least 6 months of follow up after the first injection. Baseline visual acuities ranged from 1.1 logMAR to light perception (LP) in study eyes, and 0.7 logMAR to LP in untreated contralateral eyes. After three months, one patient had a large (2.7 logMAR) improvement and four other patients had smaller improvements from baseline that were equal or greater than the 0.3 logMAR commonly considered as clinically meaningful. Interocular comparison at baseline showed treated eyes to be 0.12 logMAR (6 letters) worse than untreated eyes; by three months after intervention, however, interocular asymmetry reversed and treated eyes were 0.54 logMAR (26 letters) better than untreated eyes. Statistical analysis showed a significant effect at three months after treatment.

To better quantify changes in photoreceptor function due to intervention, the intensity of dimmest lights detected in the dark were evaluated with full-field stimulus testing (FST). Before intervention, chromatic differences were consistent with detection by cone photoreceptors in all patients but one who had function mediated by rod photoreceptors. By two and three months after the intervention, both red and blue thresholds showed improvements in many treated eyes. At baseline, there was symmetry between the eyes with interocular differences averaging less than 0.02 log. After the injections, an interocular asymmetry developed by three months favoring better thresholds in treated eyes (-0.37±0.72 log for red, -0.82±0.83 log for blue, respectively. Importantly, the large improvements of one patient were not the sole driver of the significance of the clinical trial cohort. Removing the exceptional responder from the analyses did not change the main statistical conclusion supporting significant improvements of visual acuity and FST at 3 months. The clinical trial is currently ongoing.

12) X-Linked Trial and Choroideremia Clinical Trial Update
Dr. Robert MacLaren, University of Oxford, Oxford, UK

The phase III gene therapy trial for choroideremia sponsored by Nightstar Therapeutics is ongoing and almost fully recruited. It involves treatment and referral sites in 9 countries across the continents of Europe, North America and South America. The key outcome measure is visual acuity gain in a subset of the population in advanced disease compared with controls after one year. It should be noted that the trial is only for patients with visual acuities between 6/60 and 6/12. The phase I/II clinical trial for X-linked retinitis pigmentosa caused by mutations in RPGR has also expanded from Oxford in the UK to two US sites with further planned later this year. Initial positive data showing visual field improvements in some of the treated patients in the dose escalation phase was presented at ARVO this year. The vector in this gene therapy encodes an RPGR transgene that has been codon-optimised to stabilise the ORF15 region and disable the naturally occurring splice donor site. The distinguishing feature of this particular trial is that the resulting RPGR protein is the correct full-length wildtype version and it undergoes correct glutamylation, which is a critical post-translational modification required for RPGR function.

All three trials use subretinal delivery of AAV vectors and further work has been undertaken to improve the safety of this procedure using OCT-guided surgery, intraoperative dyes and robotic delivery.

13d) Update on Treating the First Patients with RPE65 and RLBP1 Mutations Using Luxturna in Europe and CPK880 in Sweden.

Dr. Kali Stasi, Novartis Institutes for Biomedical Research, Cambridge, MA, USA

RPE65 update: In January 2018, Novartis and Spark Therapeutics entered into separate licensing and supply agreements covering development, registration and commercialization rights to and supply of voretigene neparvovec (LuxturnaTM) in markets outside the United States. Novartis is committed to ensure that patients outside the US have access to this innovative gene therapy treatment for patients with biallelic RPE65 mutation-associated retinal dystrophy, a progressive disease that eventually leads to complete blindness in the majority of patients and for whom there is no other pharmacotherapy available.

Voretigene neparvovec was approved by the EMA in November 2018 and Novartis is actively working with medical experts and reimbursement authorities to expand access to treatment to patients in multiple countries as quickly as possible. The first national reimbursement approvals are expected in 2019, specifically we expect the first countries to be Germany and France.

RLBP1 update: Retinaldehyde-binding protein 1 (RLBP1) retinitis pigmentosa (RP) is a rare progressive retinal degenerative disease currently without any treatment. It is a form of autosomal recessive RP caused by mutations in the RLBP1 gene on chromosome 15, resulting in either the absence or dysfunction of cellular retinaldehyde-binding protein (CRALBP), a protein that is important in the visual cycle. RLBP1 RP is characterized by early, severe night blindness and slow dark adaptation from childhood, followed by progressive loss of visual field, visual acuity, and colour vision. Most patients are legally blind by middle adulthood. Preclinical research was performed in Rlbp1-/- (knockout) mice with the genetic defect causing slow dark adaptation leading to night blindness, one of the typical clinical manifestations of the disease, without retinal degeneration. A single subretinal injection of self-complementary human RLBP1 genome with an adeno-associated vector (AAV) capsid improved rod mediated dark adaptation for one year, in a dose dependent fashion. (Choi VW et al. Mol.Ther.Methods Clin. Dev. 2015;2:15022). In a non-human primate study, it was shown that CPK850 at an initial subretinal dose of ~3x107 vg/µL can safely be used in clinical trials (MacLachlan TK et al Molecular Therapy: Methods & Clinical Development 2018 PMID: 29359172). A Natural History study showed no significant progression of the disease during a 2-year follow-up period (ARVO 2017 posters 3244, 3246, 3249, 3251, 3254 and 3255) and is currently soon to be completed with 5-year of follow-up. A Proof of Concept (PoC) Phase 1/2 single dose escalation trial of the AAV gene augmentation compound CPK850 (clinicaltrials.gov NCT03374657) has been initiated in one clinical site in Sweden.

14) Sugar Metabolism in Rod Cells Can Delay Degeneration in Retinal Degeneration.

Dr. Stephen Tsang, Columbia University, New York City, NY, USA

Although gene therapy has shown promise in RP, it is complicated by the fact that defects in 67 genes have been linked to the disorder and each genetic defect would require a different therapy. The present study shows that precision metabolic reprogramming can improve the survival and function of affected rods and cones in at least one type of RP. Since many, if not most, forms of the disorder have the same metabolic error, precision reprogramming could conceivably be applied to a wide range of RP patients.

Rods are among the most metabolically active cells in the body. They are particularly active during periods of darkness when they burn glucose to release energy. In earlier work, Dr. Tsang and his colleagues theorized that rods deteriorate in RP in part because they lose the daytime's ability to use glucose to rebuild the rod's outer segment. Thus, the diseased rods might be rescued by reprogramming sugar metabolism. This hypothesis was tested in mice with a mutation in the Pde6 gene that disrupts rod metabolism, leading to an RP-like disorder. The mice were treated so that their rods could not express Sirt6, a gene that inhibits glucose metabolism. Examination of photoreceptors using ERG showed that that the mice had significantly greater measures of rod and cone health than untreated controls. Overall, the metabolomes (all of the metabolites found in the organism) of the treated mice had accumulated the molecules needed to build the outer segment. In addition, the rods and cones survived longer in the treated mice than in the controls. While the treatment significantly prolonged survival of the diseased rods and cones, it did not prevent their eventual death. Thus, the next challenge is to determine how to extend the therapeutic effect of Sirt6 inhibition.

Although the treatment that was used in the mice cannot be applied directly to humans, several known Sirt6 inhibitors could be evaluated for clinical use. The inhibitors include enzyme blockers called thiomyristoyl peptides, a common plant pigment known as quercetin as well as vitexin, a substance derived from the English Hawthorn tree. Further studies are needed to explore the exciting possibility that precision metabolic reprogramming may be used to treat other forms of RP and retinal degeneration.

C) Other Business: Announcements, New Business and Conclusions

15) ERN: Ontology and CPMS: The Virtual Patient Management System. Dr. Helene Dollfus, Hospital de Hautepierre, Strasbourg, France

The European Reference Networks (ERNs) are virtual networks involving healthcare providers across Europe. The aim is to facilitate discussion and management of rare or complex diseases. ERN-EYE is a network dedicated to Rare Eye Diseases (RED). It is comprised of 29 health providers in 13 countries. As we are in the middle of the 5 first years of the projects, many initiatives are currently being developed. All our communications are centralized on a dedicated website - ***www.ern-eye.eu*.**

The creation of a virtual clinic, EyeClin, to better diagnose and treat patients, is the cornerstone of ERN-EYE. EyeClin was built thanks to a Clinical patient Management System (CPMS) common to all ERNs and provided by the EC, in addition to a new customized eye-dataset to fit ERN-EYEn needs specifically. Each specialty is clearly represented in the system and the pediatric group organizes specific regular meetings to discuss difficult cases. The launching of EyeClin will bring expertise to a large number of RED-affected EU citizens and stimulate their participation in initiatives generated or recognized by ERN-EYE such as nourishing registries, empowering research and stimulating trials.

As the first steps of the customization have been provided to the EC during the first year, the work continued during this second year to finally lead to a first release on the 8th of November, 2018. This dataset is quite extensive to allow all possible ophthalmic examination results to be entered in a standardized manner to facilitate their evaluation by the panel experts. Moreover, for each specific exam, we defined all possible terms in accordance with our previous workshop dedicated to EYE ontology and cross-linked them with HPO terms to ensure the best interoperability of systems. In addition, to ensure

adequate and efficient use of the CPMS by all ERN-EYE members, ErN-EYE set up an IT technical support desk.

To date, the Helpdesk has provided members several tools for better use of the CPMS, especially the creation of tutorials summarizing the different steps of the process of using the CPMS, video tutorials, documents as summary sheets. The Helpdesk is also performing webinars with the Working Group Leaders to train them on the application.

16) The RI Impact Programme.
Ms. Orla Galvin, Director of Stakeholder Engagement, Retina International.

Retina International is facilitating a consortium called IRD COUNTS: Inherited Retinal Dystrophies Consortium Operating for the Under-Represented for Novel Therapies and Services. IRD COUNTS is undertaking a pilot study regarding the impact of Inherited Retinal Dystrophies (IRDs) in the UK and Ireland.

Accurate data regarding the prevalence of the range of conditions which fall under the IRD classification, the impact on the individuals and families affected and the cost burden to the UK and Irish economies are lacking. This incomplete knowledge of burden and impact of IRDs hinders development and commissioning of clinical services, treatments, and the planning and implementation of clinical treatment trials. Thus, there is a need for a stronger evidence base to support value for money to regulatory bodies for treatments recently approved, and treatments progressing through clinical trials towards market.

To ensure a strategic approach to future research and service provision, it is necessary to learn more about the IRD community. The project involves 3 work packages looking at incidence and prevalence, psychological impact and financial cost to the people affected by an IRD, their parents, and society, via literature review and survey of people affected by an IRD and their parents.

17) RI World Congress: 2020 Reykjavik Iceland.

Dr. Ragnheidur Bragadottir (University of Oslo, Oslo, Norway) could not be with us at the SMAB meeting. However, she sends us the following announcement:

“On behalf of the Organizing Committee, we welcome you to the 21st Retina International World Congress in Reykjavík, Iceland, June 4th-6th in 2020. The congress will be held at the same time and at the same venue as the next Nordic Ophthalmology Congress. The retina program of both congresses will therefore be larger and the number of attendees can be expected to be higher than before.

The concert and congress hall, Harpa, is an architectonical masterpiece and has won many international prizes. Icelandic nature is famous for its beauty and this congress will be a unique opportunity for the members of Retina International, scientists and clinicians to experience the country”.

D) Final Comments – Ms. Christina Fasser

Ms. Fasser thanked all the speakers for their excellent presentations. She wished that all would have a very successful ARVO meeting and that we would all meet next year at the SMAB meeting in Baltimore, MD, USA.

Roster of Attendees at the 2019 SMAB Meeting

Attendees
Retina International Officials

SMAB co-chairman	Dr. Eberhart Zrenner
SMAB co-chairman	Dr. Joe Hollyfield
SMAB secretary	Dr. Gerald Chader
Retina International president	Mrs. Christina Fasser
Retina International CEO	Mrs. Avril Daly

Speakers
Bragadottir Ragnheidur – Norway ; Cideciyan Artur – USA; Cremers Frans – Netherlands, Dollfuss Helene – France; Fletcher Erica – Australia; Galvin Orla – Ireland; Kuppermann Baruch – USA; Larsen Michael – Denmark; Lotery Andrew – USA; MacLaren Robert – UK; Picaud Serge – France; Ribeiro Ramiro – USA; Scholl Hendrik – Switzerland; Stasi Kali – USA; Tsang Stephen – USA

Attendees

Aguirre Gustavo – USA; Andréasson Sten – Sweden; Audo Isabelle – France; Badura Franz – Germany; Bainbridge James – UK; Banfi Sandro – Italy; Birch David – USA; Bishop Paul – UK; Brady Laura – Ireland; Collins Robert – Netherlands; Cuenca Nicolas – Spain; Downes Susi – UK; Duncan Jacque – USA; Fischer Dominik – Germany; Flannery John – USA; Heon Elise – Canada; Hoyng Karel – Netherlands; Huckfeldt Rachel – USA; Kalloniatis Michael – Australia; Kjellstrom Sten – Sweden; Klaver Caroline – Netherlands; Koenekoop Robert – Canada; Laties Alan – USA; Leroy Bart Petr – Belgium; Lorenz Birgit – Germany; Mansfield Brian – USA; Marigo Valeria – Italy; McLoughlin Sarah – Ireland; Michaelides Michel – UK; Murakami Akira – Japan; Neidhart; John – Germany; Pierce Eric – USA; Porto Fernanda – Brazil; Preisig Markus – Germany; Salles Mariana – Brazil; Sallum Juliana – Brazil; Sankila Eva-Marja – Finland; Schorderet Daniel – Switzerland; Shaberman Ben – USA; Siewing Paul – USA; Simonelli Francesca – Italy; Sparrow Janet – USA; Stingl Katharina – Germany; Summer Mary – Canada; Takahashi Masayo – Japan; Toomes Carmel – UK; Tsilimbaris Miltiadis – Greece; Tumminia Santa J. – USA; Ueffing Marius – Germany; Uusitalo Hannu – Finnland; Vincent Andrea – New Zealand; Vingolo Enzo Maria – Italy; Weber Bernhard – Germany; Wie Liisa – USA; Wenzel Andreas – Switzerland;