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MEETING REPORT

# HIGHLIGHTS FROM THE ANNUAL MEETING OF THE ASSOCIATION FOR RESEARCH IN VISION AND OPHTHALMOLOGY (ARVO) 2011: VISIONARY GENOMICS

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## SUMMARY

*The Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO) was held in Fort Lauderdale, Florida, on May 1-5, 2011, where over 10,000 ocular researchers and clinicians congregated to discuss, among other things, how genomics is starting to change the landscape of the understanding and treatment of vision diseases. Here, selected presentations from this year's meeting are highlighted.*

## INTRODUCTION

If last year's meeting gave the impression of a slow downfall in the clinical investigation of new small molecules, due in part to the impressive growth of immunotherapies, this past meeting could be seen as the invigoration of chemical therapies. In addition to results from the early stages of the clinical research of some agents, data for products already launched but for which little clinical information is available were also disclosed. And all of this without forgetting about the focus on genomics of this year's meeting, including the study of biomarkers, gene therapies and population studies. This year was also the time to start to say good-bye to the city that has welcomed attendees to the ARVO meeting in recent years. Here we highlighted some of the most representative studies covering all these matters.

## HIGHLIGHTED PRESENTATIONS

### Diabetic retinopathy

The new β-adrenoceptor agonist **compound 49b** (University of Tennessee Health Science Center, Molecular Design International) exhibited potent antiapoptotic activity in the retina of rats with streptozotocin-induced diabetes by upregulating the expression of insulin-like growth factor-binding protein 3 (IBP-3; *IGFBP3*). Male rats with symptoms of diabetes induced by a single injection of streptozotocin (60 mg/kg) were treated with compound 49b (1 mM as eye drops) daily for 8 months. Compared with control animals (nondiabetic or untreated diabetic animals), rats treated with compound 49b had increased levels of IBP-3 in the retina. This effect was concomitant with a reduction in the expression of proapoptotic markers, including Bcl2 antagonist of cell death (BAD), tumor necrosis factor receptor superfamily member 6 (*Fas*), tumor necrosis factor ligand superfamily member 6 (Fas ligand; *Faslg*) and cleaved caspase-3 (*Casp3*) (1). Treatment with compound 49b also correlated with prevention of cell loss and retinal thinning at 2 months and impeded the formation of degenerate capillaries at 8 months. Amplitudes in electroretinogram (ERG) assessments appeared to return to control levels after 8 months of therapy with the agent. Compound 49b was not detectable in the plasma of rats receiving topical treatment, suggesting that it does not reach the systemic circulation. The findings support the development of compound 49b for the treatment of diabetic retinopathy (2).

A phase I trial targeted diabetic retinopathy and diabetic optical neuropathy with human allogeneic bone marrow-derived mesenchymal stem cells (**BM-MSCs**; Fyodorov Eye Microsurgery Complex Federal State Institution, Stemedica Cell Technologies), and has shown safety for allogeneic stem cell therapy for eye complications. Two women and two men with diabetes (aged 42-62 years) with early stages of diabetic retinopathy and diabetic optical neuropathy were injected intravenously with a single dose of 100 x $10^6$ allogeneic human BM-MSCs manufactured under the guidelines of current good manufacturing practice. No adverse effects were observed or reported by the participants after injection on days 1, 14 and 30, respectively, at 2, 3 and 6 months and after 1, 2 and 3 years. General blood and urine examinations during the follow-up period showed an absence of infections, interstitial pneumonia and cancer in all participants, and revealed no changes in the cardiovascular system, liver and kidney functionality. A positive reversal of hemostatic dysfunction and improvements in hemodynamics at a systemic

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level were observed as early as 2 weeks after stem cell injection. Improvements in foveal sensitivity, the functional activity of the optic nerve, pigmented epithelium layer and outer and inner nuclear layers were detected by visual acuity and ophthalmoscopic examinations, perimetry test, optical coherent tomography, eletroretinography, electrooculography and Doppler ultrasound examinations. A gradual improvement of the optic disc inflammation was recorded by optic disk color analysis. Measurements of brain-derived neurotrophic factor (BDNF) in plasma and tear fluid also signaled a steady improvement during the first 6 months after injection, which became stable during the follow-up period (3).

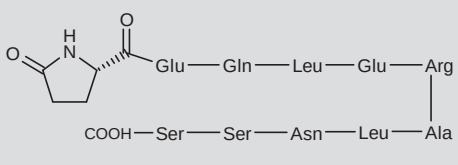
Researchers from Araim Pharmaceuticals and Queen's University of Belfast have presented promising preclinical data on **pHBSP** (Warren Pharmaceuticals), a peptide derived from helix B of erythropoietin (EPO). Sprague–Dawley rats with diabetes resulting from administration of streptozotocin for 6 months (N = 12) were randomized to treatment with pHBSP (10 μg/kg) or a control peptide given daily for 1 month by intraperitoneal (i.p.) injection. A statistically significant reduction of 50% was seen in the body weight of non-fasted rats receiving pHBSP, compared with body weight in the control group ($P < 0.001$). The levels of HbA1c in the blood of non-fasted animals treated with pHBSP exhibited a 2.5-fold increase compared with animals receiving the control peptide ($P < 0.001$). Administration of pHBSP correlated with a significant reduction in the number of acellular capillaries in the retina and decreased the expression of glial fibrillary acidic protein (GFAP) induced by diabetes in Mueller glial cells. In mice with oxygen-induced retinopathy, daily dosing of pHBSP (1, 10 or 30 μg/kg) showed no effect on preretinal neovascularization at any dose level. The results support additional investigation of the potential utility of pHBSP for the treatment of diabetes-related retinopathy (4).

### Glaucoma/ocular hypertension

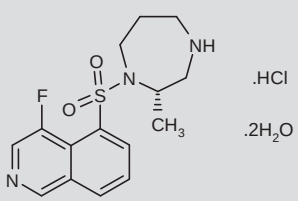
**AR-12286** is a first-in-class selective Rho-associated protein kinase (ROCK) inhibitor that lowers intraocular pressure (IOP) by increasing trabecular outflow, a mechanism distinct from other glaucoma treatments. Phase IIb data on AR-12286 were presented by scientists from Aerie Pharmaceuticals and the Mount Sinai School of Medicine. A total of 217 patients previously treated for ocular hypertension or glaucoma were enrolled in a randomized, double-blind trial comparing twice-daily 0.25% AR-12286, once-daily 0.5% AR-12286 dosed in the afternoon and once-daily latanoprost dosed in the afternoon for 28 days (see ClinicalTrials.gov Identifier NCT01060579). Adverse events were reported in 138 participants, whereby 125, 79 and 79 occurred in the respective groups. No drug-related adverse events were serious and the most common adverse events were eye disorders, which affected 55.3%, 18.6% and 25.7%, respectively, of participants receiving these respective treatments. Two subjects discontinued due to drug-related adverse events. The most notable adverse event with once-daily 0.5% AR-12286 was conjunctival hyperemia, which generally resolved during sleep. The primary endpoint of the trial was mean IOP at 8 a.m., 10 a.m., 12 p.m. and 4 p.m. on days 14 and 28, and both AR-12286 concentrations were associated with significant reductions in mean IOP at all time points on days 14 and 28. Mean IOP ranged from 18.0 to 20.4 mmHg with once-daily 0.5% AR-12286, and this regimen demonstrated superiority to twice-daily 0.25% AR-12286, with better efficacy at 8 a.m. Once-daily 0.5% AR-12286 was somewhat less effective than latanoprost, with an overall mean IOP that was 0.9 mmHg higher, a difference that was 0.5 mmHg when only responders were compared (5).

Topical application of the ROCK inhibitor **AMA-0076** (Amakem, Katholieke Universiteit Leuven) to the eye of ocular normotensive rabbits reduced IOP, suggesting a potential therapeutic benefit of the agent in glaucoma. Topical dosing of AMA-0076 (0.3% solution) 3 times daily to 15 ocular normotensive New Zealand white rabbits correlated with a significant decrease in IOP (14% on average) versus vehicle ($P = 0.038$). In rabbits with ocular hypertension induced by intracameral injection of a viscoelastic solution, repeated dosing of AMA-0076 (0.3% solution) prevented the increase in IOP ($P < 0.0001$ versus the control eye), an effect that was more pronounced than that of latanoprost (0.005%; $P = 0.0004$). Preliminary findings suggest that AMA-0076 did not cause hyperemia at doses that effectively reduced IOP, and that it did not affect the IOP of the contralateral eye, indicating low systemic exposure to the agent (6).

Encouraging preclinical and clinical results were disclosed for **K-115** (D. Western Therapeutics Institute [DWTI], Kowa), a ROCK inhibitor that is currently undergoing phase II development for the treatment of glaucoma. Unilateral topical single instillation of K-115 as a 0.1%, 0.2% and 0.4% ophthalmic solution in male cynomolgus monkeys resulted in a dose-dependent decrease in IOP. Coadministration of the agent (0.4% solution) with latanoprost (0.005% solution) in monkeys correlated with a greater reduction in IOP than latanoprost alone ($P < 0.01$). In male Japanese white rabbits, treatment with




pHBSP




K-115

K-155 (0.4% solution) was associated with a significant increase in the outflow facility of the instilled eye compared with the outflow facility of the control eye. The agent had no effect on the production of aqueous humor or uveoscleral outflow (7). In a prospective, multicenter, open-label, randomized, 3-period, Latin square crossover trial, 28 patients with primary open-angle glaucoma or ocular hypertension were randomized to receive K-155 (0.2% or 0.4% solution) or placebo twice daily at 9.00 a.m. and 9.00 p.m. The three 2-day dosing periods were separated by a washout step. The maximum decrease in mean IOP from baseline was recorded at 2 hours following instillation of K-155 at either dose level. Reductions in IOP of 6.4 and 5.3 mmHg, respectively, were seen at 11.00 a.m. in subjects treated with the 0.2% and 0.4% K-155 solutions, whereas the respective reductions in IOP at 21.00 p.m. were 4.3 and 4.2 mmHg. Conjunctival hyperemia was observed in all subjects across treatment groups. No serious adverse events and no cases of conjunctival hyperemia were reported (8). K-155 as a 0.1%, 0.2% and 0.4% solution or placebo was administered twice daily for 8 weeks to patients with primary open-angle glaucoma or ocular hypertension (N = 210) in a prospective, multicenter, randomized, double-masked, parallel-group trial. Dose-dependent reductions in IOP from baseline at 9.00 a.m. of the last visit were observed in individuals treated with K-155 (decreases in IOP of 3.4, 3.2 and 3.5 mmHg, respectively, were seen in groups treated with K-155 0.1%, 0.2% and 0.4% solution). Participants in the 0.4% dose level achieved the maximum lowering effect in IOP (5 mmHg) from baseline at 11.00 a.m. of the last visit. Acceptable safety and tolerability were reported with all tested doses of K-155 (9).

Studies conducted by investigators from Altheos and Asahi Kasei Pharma have provided an overview of the preclinical profile of the ROCK inhibitor **ATS-907**, an agent being developed to lower IOP in patients with glaucoma after topical ocular administration. $K_i$ values for inhibition of Rho-associated protein kinase 1 (p160 ROCK-1, ROCK1) were 36.0 nM for ATS-907 and 7.8 nM for ATS-907 M1, its primary metabolite, and $K_i$ values for Rho-associated protein kinase 2 (p164 ROCK-2, ROCK2) were 37.0 and 7.5 nM, respectively. ATS-907 demonstrated selectivity for Rho-associated protein kinases over 16 other protein kinases and ATS-907 M1 showed no significant inhibition of any of the enzymes evaluated. High Caco-2 cell permeability was observed for ATS-907, with approximately four times greater permeability than ATS-907 M1. The only ATS-907 metabolite in S9 liver fractions from humans, cynomolgus monkeys and Japanese white rabbits was ATS-907 M1. Rapid cellular penetration and conversion to ATS-907 M1 in the aqueous chamber was noted after single topical ocular administration of ATS-907 in Japanese white rabbits, with aqueous humor levels of ATS-907 M1 declining more slowly than those of ATS-907. ATS-907 was undetectable in plasma, while the metabolite's levels in plasma were very low (10). In normotensive New Zealand white rabbits administered single topical ocular doses of ATS-907, maximum mean reductions from baseline in IOP were –27%, –35% and –42%, respectively, at concentrations of 0.02%, 0.05% and 0.2%. Studies in normotensive Japanese white rabbits showed that increasing the pH of the ATS-907 solution enhanced the reduction in IOP. When administered twice daily for 7 days, ATS-907 was well tolerated and safe at doses of 0.1-5%, as assessed by gross ocular and clinical exams, biomicroscopy and histopathology. Dose-related conjunctival hyperemia was observed at doses of 3-5%, but resolved within 2-4 hours (11). Normotensive cynomolgus monkeys received topical ATS-907 as single and repeated doses twice daily for 14 days. Single doses of 0.05% and 0.5% were associated with dose-dependent reductions in IOP, with an effect seen as early as 2 hours after dosing and lasting over 10 hours. Reductions in IOP were –3.7 mmHg (–18%) with 0.05% ATS-907 and –4.65 mmHg (–22%) with 0.5% ATS-907; the reduction in IOP observed with latanoprost 0.005% was –2.43 mmHg (–12%). ATS-907 concentrations of 0.05% and 0.2% had similar effects in the 14-day study, with a mean maximal IOP decline of up to 4 mmHg. There were no significant tolerability or safety signals, and no evidence of inflammatory or microscopic changes was observed via histopathology on day 14 (12). ATS-907 was exclusively licensed to Altheos last year for all territories outside Japan and Korea. It will reportedly enter the clinic at the end of this year or the beginning of next year.

The Alienor (Antioxydants, Lipides Essentiels, Nutrition et maladies OculaiRes) study is a population-based epidemiological study on nutrition- and age-related eye diseases (including age-related maculopathy, cataracts, glaucoma), performed in residents of Bordeaux (France) aged 73 years or more. Regarding glaucoma, data were presented in relation to the association of metabolic syndrome with ocular hypertension and open-angle glaucoma. Volunteers complying with the inclusion criteria had an eye examination between 2006 and 2008, and of 963 subjects, 833 had complete data (1,666 gradable eyes). When subjects presented structural (vertical cup:disc ratio [VCDR] ≥ 0.7 and/or assymetry of VCDR ≥ 0.2 and/or rim width:disc ratio [RDR] ≤ 0.1) and functional (visual field with a group of three non-borderline points with $P < 0.01$ and at least one of them with $P < 0.005$) evidence, they were classified as affected by glaucoma. In the absence of open-angle glaucoma, when presenting IOP > 21 mmHg and/or IOP-lowering therapy use, they were classified as affected by ocular hypertension. The results of this study confirmed that elevated fasting glycemia (fasting blood glucose > 6.1 mmol/L and/or antidiabetic therapy) was associated with a twofold increased risk of open-angle glaucoma (odds ratio [OR] = 2.40; 95% confidence interval [CI]: 1.08-5.35; $P = 0.03$), but there was no association between open-angle glaucoma and other components of the metabolic syndrome, such as plasma triglycerides and HDL cholesterol, waist circumference and arterial hypertension. Regarding ocular hypertension, a slight association was found with fasting glycemia, but in this case it was not statistically significant (OR = 1.48; 95% CI: 0.83-2.66; $P = 0.19$). Taken as a whole, an association was not found between metabolic syndrome and open-angle glaucoma (OR = 1.23; 95% CI: 0.54-2.79; $P = 0.62$) or ocular hypertension (OR = 1.20; 95% CI: 0.72-2.01; $P = 0.49$) (13).

### Age-related macular degeneration

A single nucleotide polymorphism (SNP) in *SLC23A1*, the gene that encodes solute carrier family 23 member 1 (sodium-dependent vitamin C transporter 1), may be associated with neovascular age-related macular degeneration (NVAMD), according to results obtained in the EUREYE study. An enzyme-based assay and KASPar® technology were used to estimate the levels of vitamin C in the plasma and to perform genotypic analysis of the rs33972313 SNP of *SLC23A1* in 158 patients with NVAMD and 2,268 control subjects. In control indi-

viduals, the prevalence of the G/G, G/A and A/A genotype variants of *SLC23A1* SNP rs33972313 was established at 95.2%, 4.8% and 0%, respectively, and significantly lower levels of vitamin C were detected in the plasma of those with the G/A variant than in that of those with the G/G variant ($P = 0.02$). In analyses adjusting for factors associated with vitamin C in the plasma (such as age, sex, center, smoking, alcohol, diabetes, cardiovascular conditions and systolic blood pressure) the unadjusted ORs of NVAMD for the G/A and G/G genotypes were established at 1.56 (95% CI: 0.65-3.73) and 2.29 (95% CI: 1.24-4.22), respectively. The OR remained unaltered when the concentration of vitamin C in the plasma was factored into the model. The analysis identified no correlation between the levels of vitamin C and NVAMD, irrespective of the inclusion of the rs33972313 *SLC23A1* SNP (14).

A **monoclonal antibody targeting β-amyloid** (anti-Aβ MAb 6F6; GlaxoSmithKline) exhibited prophylactic and therapeutic effects in a mouse model of age-related macular degeneration (AMD) and may represent a therapeutic candidate for the treatment of patients with AMD or retinal dysfunction. Mice with a genetic ablation in the complement factor H gene (*Cfh*$^{-/-}$) exhibit signs of early AMD, including the formation of ocular autofluorescent deposits in the basement membrane and deposition of activated complement C3 and Aβ in the retina. Weekly administration of the monoclonal antibody against Aβ to *Cfh*$^{-/-}$ mice at 3 and 6 months of age (prophylactic and therapeutic treatment, respectively) for 12 weeks resulted in dose-dependent decreases in the autofluorescent deposits in the basement membrane and correlated with a reduction in the deposition of Aβ and complement C3 in the retina. An increase in the levels of Aβ in the serum was reported following treatment on either schedule, suggesting the removal of the protein from the retina via a peripheral sink mechanism (15).

The tolerability of FCFD-4514-S (Genentech), a recombinant humanized monoclonal Fab fragment directed against complement factor D (CFD), was evaluated in cynomolgus monkeys. Male and female animals received single and repeated doses of the antibody in the eye (1, 3, 5 and 10 mg/eye) given once every 3 weeks for a total of 10 doses. Each dose was given as 2 bilateral intravitreous injections spaced 15 minutes apart. Systemic exposure to FCFD-4514-S was found to increase with rising dose levels, and increases in mean $C_{max}$ and AUC values were roughly dose-proportional. No accumulation of FCFD-4514-S was reported after 10 doses and drug exposure was not affected by antibodies against the product. Intraocular pressure measurements, ocular photography, electroretinography, fluorescein angiography and optical coherence tomography showed no FCFD-4514-S-related adverse events. Clinical ophthalmic examinations displayed tolerability at single bilateral intravitreous doses of up to 10 mg/eye or at repeated bilateral intravitreous doses of up to 3 mg/eye for 10 doses. Repeated doses of 10 mg/eye triggered variable ocular inflammatory responses, and following six or eight doses, severe anterior and posterior uveitis were reported in two animals. Microscopic studies revealed intraocular inflammation with plasma cell infiltrates and high titers of antibodies against FCFD-4514-S within multiple structures in the eye. The results enabled the initiation of a dose-escalating phase Ia study of FCFD-4514-S administered as a single intravitreal dose to identify its maximum tolerated dose (MTD), as well as a proof-of-concept phase Ib/II trial with a safety run-in phase to study the activity of multiple intravitreal doses of FCFD-4514-S in patients with geographic atrophy associated with wet AMD (respective ClinicalTrials.gov Identifiers NCT00973011 and NCT01229215) (16).

Preliminary phase I/II data were presented on **MP-0112** (Molecular Partners), a DARPin®-based inhibitor of vascular endothelial growth factor A (VEGF-A). An open-label, randomized, non-controlled, single-group assignment phase I/II trial is evaluating MP-0112 in subjects with wet AMD, the main objective of which is to assess the agent's safety and tolerability after intraocular injection; it also aims to establish the MTD following a single injection. Participants (N = 32; 4-9/cohort) received a single intravitreal injection of MP-0112 at doses of 0.04, 0.15, 0.4, 1 or 2 mg. Treatment with the agent was safe and well tolerated, with dose-related transient sterile inflammation being the most frequent adverse event. Stable or increased visual acuity was reported in all 32 evaluable patients at the end of the 16-week follow-up period. Of the 10 subjects receiving the 1-mg dose, 8 did not have disease progression for 8 weeks. Of the 10 participants receiving 2 mg MP-0112, 7 did not have disease progression for 16 weeks (17). Quantification of the central retinal thickness and assessment of choroidal neovascularization were performed by optical coherence tomography and fluorescein angiography, respectively. Reductions in central retinal thickness by 95 and 111 μM, respectively, were seen at 4 weeks in subjects treated with MP-0112 1 and 2 mg. This effect was sustained for 12-16 weeks in 7 of 8 individuals. Dose-related reductions in vascular leakage were observed by fluorescein angiography. No leakage was reported in 62% of patients at week 4 (18). In an open-label, randomized, non-controlled, single-group assignment phase I/II study, 18 patients with diabetes-related macular edema (DME) received a single dose of MP-0112 0.04, 0.15 or 0.4 mg by intravitreal injection (ClinicalTrials.gov Identifier NCT01042678). The trial was completed by 17 participants. MP-0112 was safe and well tolerated. The most commonly reported adverse event was transient sterile inflammation that resolved without visual consequences. Improvements were observed in best corrected visual acuity (BCVA), with 4 of 17 patients gaining ≥ 15 letters at week 16 compared with baseline. Individuals in the 0.15-mg cohort displayed the highest reduction in central retinal thickness (mean decrease of 137 μM at week 4; mean reduction of 68 μM maintained up to week 12) (19). A license agreement was recently signed between Allergan and Molecular Partners for the development of MP-0112 in ophthalmic conditions.

The activity of the competitive and reversible multikinase inhibitor **SAR-397769** (Sanofi) observed in a rat model of AMD may lead to further investigation of the compound in animal models and eventually humans. In a rat model of laser-induced macular degeneration, laser photocoagulation of the retinal pigment epithelium and Bruch's membrane causes rupture of Bruch's membrane and infiltration of choroidal blood vessels towards the retina. SAR-397769, formulated in a proprietary vehicle at 0.1%, was administered topically to each eye in a volume of 30 μL/eye, with doses given once, twice or three times daily for 1 week. Oral dosing at 10 mg/kg b.i.d. was used as a control. Ocular administration was associated with very low systemic exposure, but there was high exposure in the anterior and posterior eye segments, which was comparable to that achieved with oral dosing at 0.5 hours. Levels declined in the posterior cup after 4 hours, but remained high. SAR-397769 administered via eye drops once, twice and three times daily was associated with

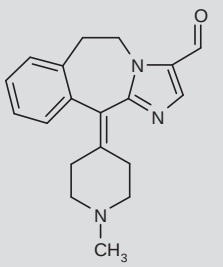
reductions in choroidal neovascularization volume, with reductions in mean volumes of 51.6%, 63.2% and 67.6%, respectively, while the reduction with twice-daily oral dosing was 63.4%. Finally, clinical observations indicated that the SAR-397769 eye drops were well tolerated (20).

As mentioned above, the Alienor study is a population-based epidemiological study on nutrition and age-related eye diseases. Regarding age-related maculopathy (ARM), at this year´s meeting three substudies were presented. In all three, ARM was classified in five stages using color photographs: late neovascular ARM, late atrophic ARM (geographic atrophy), early ARM2 (large soft indistinct drusden and/or reticular drusden and/or large disctinct drusden with pigment abnormalities), early ARM1 (large soft distinct drusden alone or pigment abnormalities alone), and no ARM. In the first of the substudies, plasma carotenoids were determined from blood samples collected from subjects between 1999 and 2001. The samples were kept frozen at –80 °C, until the eye examination that took place between 2006 and 2008. Of 963 subjects, 662 (1,281 eyes) had complete data. It was found that subjects with higher plasma levels of lutein or combined lutein and zeaxanthin had a higher risk of early ARM2 (respective OR = 1.32; 95% CI: 1.04-1.66; $P = 0.02$ and OR = 1.32; 95% CI: 1.05-1.65; $P = 0.02$). The same trend was found for zeaxanthin, but association was not statistically significant (OR = 1.16; 95% CI: 0.98-1.36; $P = 0.08$). No association was found between other stages of ARM and lutein and zeaxanthin (21). In the second of the substudies, the focus was to determine if autofluorescence imaging (AF) could be effectively used to detect reticular drusden, which is a risk factor for the development of ARM. Of 69 eyes classified as definitive reticular drusden by AF imaging, 69.9% (42 eyes) were not detected by color photographs. On the contrary, of 24 eyes classified by color photographs as definite reticular drusden, only 1 eye (4.2%) was absent by AF, 1 (4.2%) was questionable and 22 (91.7%) had the same diagnostic. In relation with ARM and using AF, it was detected that 29.3% of early ARM2 eyes had definite reticular drusden, 10.8% of the early ARM1 eyes and 3.4% of those without ARM. Meanwhile, the percentages according to color photographs were 17.1%, 0% and 0%, respectively (22). In the third substudy, the association of age-related maculopathy susceptibility protein 2 (*ARMS2*) with ARM was studied by establishing the A69S polymorphism (rs10490924) from blood samples obtained between 1999 and 2001. A total of 738 subjects (1,424 eyes) had complete data. This population-based study corroborated the contribution of the TT genotype of *ARMS2* A69S polymorphism in early ARM1, early ARM2, late atrophic ARM and late neovascular ARM (OR = 4.60; 95% CI: 1.54-13.7; $P = 0.006$; OR = 13.8; 95% CI: 5.17-36.7; $P < 0.0001$; OR = 23.6; 95% CI: 5.28-105.7; $P < 0.0001$; and OR = 16.1, 95% CI: 3.32-78.6; $P = 0.0006$, respectively). The GT genotype was only statistically associated with early ARM1 (OR = 1.52; 95% CI: 1.03-2.23; $P = 0.04$). All these association were independent from smoking and CFH Y402H polymorphism, two well-known ARM risk factors (23).

### Other disorders

UshStat® (Oxford BioMedica) is a gene therapy for the treatment of Usher syndrome type 1B, based on the equine infectious anemia virus (EIAV)-based lentiviral vector designed to encode the human MYO7A protein. Results of the subretinal delivery of UshStat in *shaker1* mice, a mouse model of the disease, and of its impact on photoreceptor function in response to different light intensities were presented. Treatments subretinally delivered consisted of EIAV CMV GFP, EIAV CMV MYO7A (UshStat) or formulation buffer. Photoreceptor function was determined histologically and neuroprotection from photoreceptor degeneration in response to chronic light intensity, as well as protection from light-induced superoxide accumulation, were measured. Gene transfer and expression in photoreceptors and retinal pigment epithelial cells after subretinal delivery was proven, and UshStat was also found to reduce photoreceptor cell loss and DHE staining, as well as restore the threshold for translocation of alpha-transducin in the photoreceptors (24).

Results of in vivo and in vitro studies of **alcaftadine** (Vistakon Pharmaceuticals), a histamine $H_1$ receptor antagonist, were discussed in several presentations. Using a modified conjunctival allergen challenge (CAC) mouse model, alcaftadine was compared to olopatadine for its ability to modify epithelial cell changes associated with allergic conjunctivitis. Both compounds were effective at improving acute allergy signs, as proven by the similar mast cell counts found in animals treated with both drugs, but only alcaftadine-treated animals had lower conjunctival eosinophil infiltration. Furthermore, alcaftadine prevented the significant decrease in the expression of the junctional protein ZO-1 caused by the allergen challenge. These results indicate that alcaftadine presents therapeutic properties in addition to its antihistamine action (25). Alcaftadine was further characterized in vivo and in vitro. In vivo, it attenuated the eosinophil influx in a dose-dependent manner in a guinea pig model of conjunctivitis. In vitro, it was found to have high affinity for the human histamine $H_1$ ($K_i = 3.1$ nM) and $H_2$ ($K_i = 62$ nM) receptors, and to also act as an antagonist at the human histamine $H_4$ receptor ($K_i = 2.9$ µM). Taking into account these characteristics, alcaftadine may be considered a new class of therapy for the treatment of allergic conjunctivitis (26). In a CAC clinical model, the effectiveness of different doses of alcaftadine ophthalmic solutions (0.05%, 0.1% and 0.25%) were compared against placebo and an active comparator (olopatadine hydrochloride 0.1% ophthalmic solution). The study consisted of 4 visits: 1 and 2 were screening visits to perform the CAC and select the subjects for the study, and 3 (day 0 ± 3) and 4 (day 14 ± 3) were treatment visits in which the CAC was repeated. A total of 164 patients of 170 completed the study. Signs and symptoms of allergy, including ocular itching and conjunctival redness were evaluated. Alcaftadine 0.25% ophthalmic




Alcaftadine

solution demonstrated a rapid onset of action (15 minutes) and prolonged duration of action (16 hours). For conjunctival redness, both alcaftadine 0.25% and olopatadine 0.1% treatments resulted in significantly lower mean scores compared to placebo at visits 3 and 4. At visit 3, lower mean ocular itching scores were found in patients treated with all three alcaftadine concentrations compared to olopatadine- and placebo-treated subjects. At visit 4, all active treatment groups were clinically (≥ 1 unit difference) and statistically ($P < 0.001$) superior to placebo regarding ocular itching scores. Alcaftadine was found to be well tolerated, with mild adverse events reported. All the previous results confirm alcaftadine 0.25% as a suitable once-daily treatment choice (27). Alcaftadine was also evaluated in a multicenter, 2-arm, placebo-controlled phase III trial involving patients at least 10 years old with a previous history of allergic conjunctivitis (ClinicalTrials.gov Identifier NCT00889330). The objective of the study was to evaluate the safety and efficacy of the alcaftadine 0.25% ophthalmic solution. A CAC was performed at visits 3 and 4, respectively, after 16 hours and 15 minutes from treatment, and ocular and nasal symptoms of allergy were then graded, including ocular itching and conjunctival redness. The percentage of patients with minimal itch in the alcaftadine groups 3 minutes after allergen challenge was 87% at visit 3 and 97% at visit 4. Alcaftadine was also found to significantly reduce conjunctival redness, as well as certain other allergic signs and symptoms (28).

## DISCLOSURES

The authors state no conflicts of interest.

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