

## CLINICAL NEWS

# Lilly to Appeal FDA's Decision Requiring Additional Ruboxistaurin Study

Indianapolis drug maker Eli Lilly and Company will appeal the US Food and Drug Administration's (FDA) decision to require Lilly to do another trial for ruboxistaurin, according to the company.

In September, Lilly received an approvable letter from the agency, but it indicated that it will require efficacy data from an additional phase 3 study before it will consider approving the molecule. The new patient trial could

take up to 5 years to complete.

Lilly has decided to appeal the FDA's decision and has recently begun talks with the agency, according to a news release. Lilly reached this decision by considering the significance of the unmet medical need that diabetic retinopathy presents, the efficacy demonstrated in the completed clinical studies and the robust safety profile shown in >3,300 patient-years of clinical trial exposure.

## MARINA Study Shows Improvements for AMD

Monthly intraocular injections with 0.5 mg ranibizumab (Lucentis; Genentech, San Francisco) resulted in stable or improved visual acuity in 95% of patients after 1 year, and in 90% of patients after 2 years.

These results from the first phase 3 multicenter clinical study to show vision improvement in patients with age-related macular degeneration (AMD), known as the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA) Study, were published in *The New England Journal of Medicine*. Results showed that improvement in visual acuity was evident 1 month after the first injection; the improvement continued through 3 months and was sustained through 2 years. Overall, 34% of patients experienced a significant improvement in vision of three lines or more after 1 year and 33% of patients after 2 years — compared with 5% and 3% of controls who were not injected. After 2 years, >40% of patients had vision of 20/40 compared with 6% of the control patients. Moreover, 48% of the controls were legally blind after 2 years compared with 15% of the ranibizumab-treated patients.

"What makes this publication particularly significant is that the MARINA study was the first phase 3 study for wet AMD to show visual improvement in the aver-

age patient after 1 year of treatment, and this benefit was maintained through 2 years and associated with anatomic improvements that further confirm the effectiveness of ranibizumab," said Philip J. Rosenfeld, MD, PhD, in a news release. Dr. Rosenfeld, professor of ophthalmology at the University of Miami's Bascom Palmer Eye Institute, is also a member of the RETINA TODAY editorial board.

## NEI Funds AMD Research of Ranibizumab, Bevacizumab

The National Eye Institute (NEI) of the National Institutes of Health (NIH) will fund a new multicenter clinical trial comparing ranibizumab and bevacizumab (Avastin; Genentech, San Francisco) currently used to treat advanced AMD, according to a news release.

Ranibizumab was approved earlier this year by the FDA, based on evidence from clinical trials showing it slows the rate of progression of vision loss from AMD. In addition to the low rate of developing vision loss, approximately one-third of patients treated in these trials had improved vision at 12 months.

The FDA has approved bevacizumab for the treatment of colorectal and nonsmall cell lung cancer, but not specifically for ophthalmic uses. Bevacizumab, however, has been widely used off-label to treat advanced AMD. The new comparative study will assess the relative safety and effectiveness of both ranibizumab and bevacizumab.

NEI-supported research has helped establish that vascular endothelial growth factor (VEGF) is an important part of the biological pathways involved in triggering and sustaining the growth of new blood vessels in the retina. Research also demonstrated that VEGF is present in higher levels in a number of eye diseases (eg, AMD). NEI has supported >300 research studies at a cost of nearly \$95 million to better understand the role of VEGF in eye diseases. Two anti-VEGF therapies (ie, ranibizumab and pegaptanib [Macugen; OSI/Eyetech and Pfizer, New York, NY] have already been FDA approved specifically for the treatment of advanced AMD.

## Visual Aid Improves Tunnel Vision

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Scientists at Schepens Eye Research Institute, an affiliate of Harvard Medical School, have a device that may improve the visual abilities of people with tunnel vision.

The first study evaluating the device showed significant increases in the effectiveness and speed with which visually impaired patients found objects. The study showed that this device, which combines a tiny camera, pocket-sized computer and transparent computer display on a pair of glasses, may offer the most effective assistance to date for this patient population, according to a news release. Developed with the help of Microoptical (Westwood, Mass), the device allows the patient to see detailed visual information through the transparent display while also viewing a superimposed small outline version of a wider visual field. The tiny computer-video system provides updated outline information 30 times per second. When a patient becomes aware of a possible obstacle or important object in the superimposed outline range, he or she can move their head and eyes to look directly at the object through the display.

Twelve patients with tunnel vision were asked to find targets that were projected outside their residual visual fields. The researchers found that the search directness was greatly improved for all patients when the device was used. They also found a 22% reduction in search time in patients with a visual field wider than 10 degrees.

## Study Will Evaluate Effects of Antioxidants on AMD

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The NIH will sponsor a nationwide study to see if a

modified combination of vitamins, minerals and fish oil can further slow the progression of vision loss from AMD. This new study, the Age-Related Eye Disease Study 2 (AREDS2), will build upon results from the first AREDS study, conducted 5 years ago. That study found that high-dose antioxidant vitamins and minerals (eg, vitamins C and E, beta carotene, zinc and copper) taken orally, reduced the risk of progression to advanced AMD by 25% and the risk of moderate vision loss by 19%.

AREDS2 will refine the findings of the original study by adding lutein and zeaxanthin (plant-derived yellow pigments that accumulate in the macula and omega-3 fatty acids DHA) and EPA (derived from fish and vegetable oils) to study the formulation. The main study objective is to determine if these nutrients will decrease a person's risk of progression to AMD. Previous observation studies have suggested these nutrients may protect vision.

"Vision loss from AMD is an important public health issue. This study may help us find a better way to treat this devastating disease," said Elias Zerhouni, MD, director of the NIH, in a news release.

Emily Chew, MD, study chair and deputy director of the Division of Epidemiology and Clinical Research at the NEI, says they are seeking 4,000 people aged 50 to 85 years with AMD in both eyes or advanced AMD in one eye for the AREDS2 study. They must be available for yearly eye examinations for at least 5 years. For a list of study centers, eligibility requirements and other information, please visit [www.nei.nih.gov/AREDS2](http://www.nei.nih.gov/AREDS2) or call 877-273-3780.

## 6-Year Progression of DR High in Blacks With Type 1 Diabetes

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Among black patients with type 1 diabetes, the 6-year rate of diabetic retinopathy (DR) progression is high, according to a report in the *Archives of Ophthalmology*.

In 483 patients from the New Jersey 725 study, 56.1% of those at risk showed a progression of diabetic retinopathy, 15% showed progression to proliferative DR (PDR) and 15.9% developed macular edema, wrote Monique S. Roy, MD, from the Institute of Ophthalmology and Visual Science, University of Medicine and Dentistry, New Jersey Medical School, Newark, and colleagues.

"A baseline high glycosylated hemoglobin level and

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systemic hypertension were significant risk factors for progression of DR, progression to [PDR] and incidence of macular edema," Dr. Roy wrote. Progression to PDR was significantly associated with a baseline older age, renal disease and severity of DR.

The incidence of macular edema was significantly associated with baseline older age, low socioeconomic status, severity of DR and total serum cholesterol level, the investigators found.

As part of the New Jersey 725 study, 483 black patients who were diagnosed with type 1 diabetes and treated with insulin before age 30 years underwent reexamination as part of a 6-year follow-up. Dr. Roy reported that the evaluations included a structured clinical interview, ocular examination, seven stereoscopic fundus photographs and blood pressure measurements.

"The severity of DR was determined via masked grading of fundus photographs," the investigators wrote. The patients also had blood and urine tests.

"At the 6-year evaluation, 72.3% of the patients at risk for incidence of diabetic retinopathy had developed any diabetic retinopathy," reported Dr. Roy and colleagues. "Because glycemic and blood pressure control in this population are poor, measures to improve medical care and ensure regular dilated eye examinations to detect vision-threatening diabetic retinopathy may reduce morbidity from the disease," the authors concluded.

## DNA May Cause Multigene Macular Degeneration

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Following reports of a gene variant strongly linked to AMD, a team of University of Michigan scientists has identified 20 variants of the same gene that show an even stronger association with the disease. The team of researchers also reported that the noncoding DNA around the gene might be the primary source of the trouble, according to a news release. They examined 84 genetic differences in and around the Complement Factor H (CFH) gene in 726 patients with AMD and in 268 unaffected people. The study included 235 pairs of relatives, including siblings and parent-child pairs.

"The [CFH] gene is extremely important," said Goncalo Abecasis, MD, the Harold F. Falls Collegiate Professor of Ophthalmology and Visual Sciences. "We simply need a closer look at what is actually happening around that gene. Perhaps these new variants cause dis-

ease by regulating levels of activity or expression of the gene, or perhaps they affect other genes."

None of the 84 genetic variants studied seemed to account for macular degeneration by itself. Instead, the variants seem to make multiple distinct contributions. The researchers found variants appeared to be organized into one of four common haplotypes. Two of the haplotypes were found to increase disease susceptibility, and two decreased it. There was also an array of relatively rare haplotypes that did not fit into one of the four groups and that were also associated with increased susceptibility.

What the researchers infer from this pattern is that there are multiple changes of DNA in the region of the CFH gene that can lead to the susceptibility and that, because they are noncoding regions of the DNA, they may be involved in some sort of regulatory function.

## Retinal Vascular Caliber and Risk of Retinopathy in Type 1 Diabetes

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Larger retinal arteriolar caliber predicts incident retinopathy in children and adolescents with type 1 diabetes, independent of conventional risk factors for retinopathy, according to findings published in *Ophthalmology*. Measurements of retinal vascular caliber may provide prognostic information regarding the subsequent risk of diabetic retinopathy, the study concluded.

Patients and controls were selected from a cohort of children and adolescents aged 12 to 20 years with type 1 diabetes, who developed incident DR (n=166) after at least 1 year of follow-up (at least two clinic visits). Controls were patients who had not developed retinopathy (n=165) after  $\geq 2$  years of follow-up (at least three clinic visits). The study showed that incident retinopathy cases had retinal arteriolar calibers (mean  $\pm$  standard deviation  $206.5 \pm 18.4 \mu\text{m}$ ) significantly larger than those of controls ( $200.2 \pm 16.5 \mu\text{m}$ ) ( $P=.004$ ) but similar retinal venular calibers ( $329.1 \pm 14.7 \mu\text{m}$  in cases versus  $326.4 \pm 15.1 \mu\text{m}$  in controls,  $P=.312$ ).

## Bevacizumab-Treated Eyes Evaluated for Inflammation

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A study of intravitreal bevacizumab administration showed no inflammatory response from the procedure

during a 1-week follow-up. During the study, 61 consecutive patients with neovascular AMD were given 1 mg bevacizumab by means of intravitreal injection and examined 1 day and 1 week after the injection. The anterior chamber inflammatory activity was evaluated using biomicroscopy and the laser flare meter (Kowa FM-500; Kowa Company, Tokyo.)

None of the patients involved had significant clinically detectable inflammatory response within the 1-week of follow-up. Anterior chamber inflammatory activity measured by the laser flare meter ranged from 1.9 counts/millisecond to 70.0 counts/millisecond (mean  $\pm$ SD,  $13.2 \pm 16.9$  counts/millisecond; [CI 95%], 7.8-18.6) before treatment. One day and 1 week after injection, values were between 3.2 counts/millisecond and 30.0 counts/millisecond (mean  $\pm$ SD,  $9.1 \pm 6.2$  counts/millisecond; [CI 95%], 7.2-11.1) and 2.0 counts/millisecond and 25.1 counts/millisecond (mean  $\pm$ SD,  $7.3 \pm 4.6$  counts/millisecond; [CI 95%], 5.8-8.8), respectively. There was a significant reduction of anterior chamber flare at 1 week compared with baseline ( $P=.031$ ).

This study was published in *Retina*.

## Optical Coherence Tomography May Detect Cystoid Macular Edema

Researchers believe optical coherence tomography (OCT) is a valuable tool in the detection and follow-up of cystoid macular edema (CME) in patients with retinitis pigmentosa (RP). In addition, treatment with acetazolamide resulted in marked improvement in OCT-diagnosed CME in RP.

In another recent study published in *Retina*, researchers treated 29 RP patients with acetazolamide (125 mg/day or 250 mg/day for 4 months to 12 months) and found that 10 patients had CME diagnosed by OCT. Of these patients, five had various degrees of fluorescein leakage by fluorescein angiography. After treatment, six patients had significant decreases in macular edema in at least one eye by follow-up OCT. In six patients, visual acuity improved by at least one line in at least one eye. The change of central foveal thickness shown by OCT was significantly correlated with the change of logMAR of BCVA (Pearson correlation coefficient [ $r$ ]=.576;  $P=.008$ ).

Researchers observed no difference in the change of

central foveal thickness by OCT and in the change of logMAR of BCVA between patients treated with 125 mg/day acetazolamide and those treated with 250 mg/day acetazolamide.

## Pilot Program Studied Anecortave Acetate Treatment

Anecortave acetate treatment of retinal angioma-tous proliferation (RAP) can reduce capillary permeability, however, it does not slow the progression of neovascularization or vision loss, according to research published in *Retina*.

Researchers studied 34 patients with RAP, administering three quantities of anecortave acetate sterile suspension among the group (ie, 30 mg, 15 mg, 3 mg). The study found that the detachment of the neurosensory retina and retinal pigment epithelium improved in all eyes. Neovascular lesions increased in size, however. Vision loss occurred in the majority of the study eyes ( $n=64.7\%$ ) independent of the concentration administered, showing that despite the improvement of the exudation, there is still a progression of neovascularization with anecortave acetate treatment.

## Study Examined Sutureless Vitrectomy, Endophthalmitis

Physicians from the Cole Eye Institute in Cleveland studied the possibility of developing endophthalmitis after transconjunctival sutureless vitrectomy using a 25-gauge system. Although the sutureless vitrectomy system obviates the need for conjunctival peritomy and decreased surgically induced trauma at entry sites, a sutureless wound may allow entry of extraocular fluid and predispose a patient to postoperative endophthalmitis. Researchers found that endophthalmitis is generally rare, occurring in  $<0.10\%$  of cases, however, recent concerns of increased frequency of postoperative endophthalmitis after sutureless clear corneal cataract extraction raise similar potential concerns for patients after sutureless vitrectomy. Even though sclerotomy incisions made by transconjunctival sutureless vitrectomy are smaller than sutureless incisions in cataract surgery (0.5 mm versus  $>2.5$  mm) and covered with conjunctiva, the possibility for wound leakage and endophthalmitis still exists.

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According to the study published in *Retina*, researchers found that in a series of 47 consecutive patients with a clinical diagnosis of endophthalmitis, cultures were positive for only 57.4% of patients. Therefore, the authors warn vitreoretinal surgeons to be aware of this potential complication, especially if there is any question about the self-sealing properties of the incision sites.

## Exercise Can Reduce AMD Risk

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Researchers from University of Wisconsin have discovered a link between an active lifestyle and lower risk of developing AMD. According to results from 4,000 men and women in Beaver Dam, Wisc, exercise and walking could reduce chances of developing AMD.

“Engaging in an active lifestyle or walking more . . . reduced the risk of developing exudative AMD over 15 years by 70% and 30% respectively,” wrote Michael Knudtson in the *British Journal of Ophthalmology*.

Knudtson and researchers studied the impact of exercise on men and women with AMD. Participants, aged 43 to 86 years, were questioned about how much exercise they did and were also assessed every 5 years. About 25% had an active lifestyle and about the same number climbed more than six flights of stairs each day.

### INDUSTRY AND BUSINESS NEWS

## New Telemedicine Application Detects Eye Condition Quickly

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A new technology called the Retcam II (Clarity Medical Systems, Pleasanton, Calif) helps to diagnose retinopathy of prematurity (ROP) an average of 2 weeks earlier than traditional methods. Previously, the only way to examine a child was to perform bedside examinations with an indirect ophthalmoscope. A doctor would then take notes and draw pictures to use as a benchmark for future examinations of that child. Combined with a new network called Stanford University Network for Diagnosis of Retinopathy of Prematurity, doctors can now obtain computerized images of the retina without visiting the patient.

The new network is the first of its type at an academic center, arriving at a critical time. Growing numbers of at-risk infants — about 60,000— coupled with more inclusive recommendations for screening brings pressure to the doctors. New guidelines implemented in February 2006 by the American Academy of Pediatrics and the American Academy of Ophthalmology, together with the American Association for Pediatric Ophthalmology and Strabismus, recommended ROP screening for any child born at  $\leq 32$  weeks of gestation or weighing  $< 1,500$  grams. This is a significant change from the 2001 guidelines that included the same weight criterion but recommended screening babies born at fewer than 28 weeks. The expanded screening criteria come at a time when the number of ophthalmologists who specialize in ROP has been steadily declining.

One solution to the screening crisis is the Retcam II, a handheld fiber optic camera connected to a wheeled console with a control panel and color video monitor. Physicians or nurses who have been trained on the Retcam II can quickly and safely scan an infant’s eye in about 5 minutes. This enables digital image files to be sent to doctors at remote locations.

“If you consider a human being directly examining the eye to be the gold standard, the Retcam Digital System had 100% sensitivity and 97% specificity in the PhotoROP trial. This means that it identified all the referral-warranted disease all of the time, and that only 3% of the time, did it suggest disease in healthy eyes,” said Darius Moshfeghi, MD, a pediatric retina specialist at Lucile Packard Children’s Hospital, in a news release.

## Bausch & Lomb Licenses Plasmin

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Bausch & Lomb (Rochester, NY) was granted a license by Talecris Biotherapeutics (Research Triangle Park, NC) for recombinant Plasmin for use in ophthalmology. The companies will codevelop Plasmin, a recombinant derivative for use in developing novel therapies for ocular conditions. Bausch & Lomb is enrolling patients in early-stage clinical trials to evaluate Plasmin’s therapeutic potential to relieve retinal traction.

“Bausch & Lomb is actively pursuing new compounds, new therapies and technologies to treat diseases that rob people of their sight,” said Praveen Tyle, PhD, Bausch & Lomb chief scientific officer and senior

vice president, global research and development. "This agreement is significant because it gives us the opportunity to develop a next-generation recombinant version with potential to reach more global markets."

## Advanced Refractive Achieves Early Milestone

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Ocular Therapeutics, a subsidiary of Advanced Refractive Technologies (ART; San Clemente, Calif) reached an important milestone in its development of a treatment for AMD.

Completion of this important phase of the manufacturing process for LD22-4 has occurred, and preclinical testing will now begin. Production of recombinant LD22-4 has proven to be efficient and economical, employing the FDA-approved protocols suitable for preparing the compound for future clinical tests. The ability to produce the LD22-4 at these levels, appropriate for pharmaceutical distribution at low cost, is one significant advantage of LD22-4 when compared with competing therapies.

"This important early step has given added impetus to rapidly bring this potentially breakthrough agent to the ophthalmology market," said Randy Bailey, president of ART, in a news release. "We are now ready to begin preclinical trials of LD22-4 and are excited to test the capabilities of this new entity."

The safety and efficacy testing, including toxicology testing and the establishment of therapeutic dosage, will be performed by Charles River Laboratories (Boston).

## Use of Renu With Moistureloc May Result in Need for Corneal Transplants

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A US research report revealed that one-third of patients with a serious eye infection associated with the Renu with Moistureloc product (Bausch & Lomb) had such severe infections that they had or will need a corneal transplant. A report published in the *Journal of the American Medical Association (JAMA)* found that individual user practices were not the only factor in the incidences of *Fusarium* keratitis associated with Renu with Moistureloc.

The study was based on 164 confirmed cases of

*Fusarium* keratitis in 33 states. Sixty-nine percent of patients had used Renu with Moistureloc compared with 15% of controls. Researchers did not find *Fusarium* at the factory or warehouse, or in unopened solution bottles.

The *JAMA* study does not examine those users who were infected before June 2005 and after April 2006. It also does not account for the users who were treated for eye-related medical issues but were not diagnosed as specifically being infected with *Fusarium* fungus.

## Pfizer Expands Ophthalmology Research

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Pfizer (New York, NY) will acquire an exclusive license to Quark's (Fremont, Calif) novel human gene RTP-801 and to molecules that modify its expression or function. RTP-801 is involved in the development of pathologic blood vessels, which accelerate the progression of AMD. The target for RPT-801 is neovascular AMD.

"Despite advances in research and the availability of new treatment options, there remains a need for new approaches to improve the lives of patients with AMD," said Martin Mackay, PhD, Pfizer senior vice president, in a news release. "We are excited about the potential of RPT-801 to preserve vision in patients with wet AMD who have an increase risk of progressive eye damage and vision loss."

## Macusight Studies Novel Drug

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Macusight (Union City, Calif) will hold phase 1 of a study of its lead product candidate in patients with diabetic macular edema. This trial, which enrolls to total of 30 patients, is designed to evaluate the safety and tolerability of Macusight's proprietary formulation of sirolimus (rapamycin) when administered in various doses through two types of ocular injections.

Investigators for this randomized, open-label, dose-escalation study will treat patients with a single subconjunctival or intravitreal injection of the sirolimus formulation. The trial will include six treatment arms with patients receiving one of three doses of sirolimus via subconjunctival injection or one of three doses of sirolimus and will provide the patient with exposure to the compound for up to approximately 3 months. ■