

## CLINICAL NEWS

# Ruboxistaurin Gets Approvable Letter

The US Food and Drug Administration (FDA) has sent an approvable letter to Eli Lilly and Company (Indianapolis) for ruboxistaurin (proposed trade name Arxxant), the company's investigational oral therapy being studied for the treatment of moderate-to-severe nonproliferative diabetic retinopathy (NPDR).

The FDA requested submission of additional data to support the clinical evidence presented by Lilly in a new drug application (NDA) that was submitted in February. According to a Lilly news release, the company plans to meet with the FDA to determine if the request can be met with data from an ongoing study or whether a new study is required.

"We will be working closely with the FDA to address

issues outlined in the approvable letter and to define the pathway forward," said Timothy R. Franson, MD, vice president of global regulatory affairs for Lilly.

Ruboxistaurin works by limiting the overactivation of protein kinase C (PKC) beta, a naturally occurring enzyme that has been linked to the development of DR.

To read more about recent clinical trial results associated with ruboxistaurin, please see page 21 of this issue, the RETINA TODAY Summer 2006 issue, page 25 or visit the archives online at [www.retinatoday.com](http://www.retinatoday.com). You may also read more about ruboxistaurin and the PKC pathway in our sister publication, DIABETIC MICROVASCULAR COMPLICATIONS TODAY, online at [www.diabeticmc.com](http://www.diabeticmc.com).

## Vegetable Pigments May Help Protect Against Age-Related Vision Loss

Women aged <75 years who eat a diet rich in the yellow plant pigments lutein and zeaxanthin may have a reduced risk of developing AMD, according to a report in *Archives of Ophthalmology*.

Previous studies have suggested a potential link between AMD and lutein and zeaxanthin, plant pigments known as carotenoids. They are found in leafy green vegetables, corn, egg yolks, squash, broccoli and peas. These compounds may reduce the risk of AMD by (1) absorbing blue light that could damage the macula, (2) preventing free radicals from damaging eye cells and (3) strengthening eye cell membranes.

Suzen M. Moeller, PhD, from the University of Wisconsin in Madison, and colleagues from the Carotenoids in Age-Related Eye Disease Study (CAREDS) Research Study Group, assessed the effects of dietary lutein plus zeaxanthin in 1,787 women aged 50 to 79 years in Iowa, Wisconsin and Oregon. The women with the highest and lowest dietary intakes of lutein and zeaxanthin in the Women's Health Initiative (WHI) were recruited to participate in CAREDS.

The WHI, launched in 1991, consisted of a set of

clinical trials and an observational study, which together involved 161,808 generally healthy postmenopausal women. The clinical trials were designed to test the effects of postmenopausal hormone therapy, diet modification and calcium and vitamin D supplements on heart disease, fractures and breast and colorectal cancer.

At the beginning of CAREDS, participants filled out a questionnaire to evaluate what their diets were like 15 years before the beginning of the study. Blood samples were taken to assess levels of carotenoids and retinal photographs were used to determine the presence and progression of AMD.

The investigators found that a higher intake of lutein plus zeaxanthin was associated with a lower risk of intermediate-stage AMD in women aged <75 years who had a stable intake of the carotenoids over the 15-year period and did not have previous AMD or a chronic disease (eg, cardiovascular disease, diabetes or hypertension) that might alter their dietary habits. No significant difference was observed, however, in the overall group of women or when comparing lutein and zeaxanthin levels in the blood to AMD occurrence. There was a weak association between dietary lutein plus zeaxanthin and advanced-stage AMD in all the women and in women aged <75 years.

The investigators wrote that the lack of a link between intake of carotenoids and AMD in the overall

study group could be due to several factors, including the fact that the older women who participated in the study may have been more likely to have consumed higher levels of fruits and vegetables during their lifetime than other older adults who have already died. Many nutrients may work together to provide protection against AMD, and the study may not have measured other dietary deficits that influence risk, the authors said.

“This exploratory observation is consistent with a broad body of evidence from observational and experimental studies that suggests that these carotenoids may protect against AMD,” they concluded. “Still, given the numerous analyses performed in this study, our results could be due to chance. More conclusive evidence from long-term prospective studies and clinical trials is needed to determine whether the intake of macular carotenoids themselves, or as markers of broader dietary patterns, can protect against intermediate AMD or delay progression in individuals who have early stages of the disease.”

## Diet High in Fish Fatty Acids Protects Against ARM

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A regular diet high in n-3 polyunsaturated fat, especially from fish, offers protection against early and late age-related maculopathy (ARM) suggests a study of an older Australian cohort. According to the authors, also reporting in *Archives of Ophthalmology*, the study could not confirm the deleterious effects of higher polyunsaturated fat intakes reported by other clinic-based studies.

To look at the relationship between diet and ARM, the investigators used data from the Blue Mountains Eye Study, which included 3,654 patients aged  $\geq 49$  years in 1992 to 1994. After 5 years, 2,335 (75.1% of survivors) were reexamined (1997 to 1999).

Dietary data were collected from 2,895 patients (79%) at baseline using a semiquantitative food frequency questionnaire to calculate dietary fat intakes. Presence of ARM was graded from retinal photographs using the Wisconsin ARM Grading System. Logistic regression adjusted for age, sex, vitamin C intake and smoking.

Patients with the highest versus the lowest quintiles of n-3 polyunsaturated fat intake had lower risk of incident early ARM (OR 0.41, [95% CI, 0.22-0.75]). A 40% reduction of incident early ARM was associated with fish consumption at least once a week (OR, 0.58

[95% CI, 0.37-0.90]), whereas fish consumption at least 3 times per week could reduce the incidence of late ARM (OR, 0.25 [95% CI, 0.06-1.00]). The authors found no association between incident ARM and butter, margarine or nut consumption.

## Hormone Therapy Not Linked to AMD

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Treatment with conjugated equine estrogens (CEE), either alone or combined with progestin, does not affect the overall risk of AMD, according to data from the WHI Sight Exam Study. A subgroup analysis found, however, that CEE plus progestin may reduce the risk of soft drusen or neovascular AMD, the authors wrote in the *Archives of Ophthalmology*.

In this ancillary study to the WHI clinical trial of hormone therapy, 4,262 women aged  $\geq 65$  years had fundus photography for the determination of AMD. Women were recruited from April 2000 to June 2002 at 21 clinical sites an average of 5 years after randomization. The women were randomized to treatment with CEE, CEE plus progestin or placebo. The women had been treated for an average of 5 years at the ophthalmic evaluation for AMD.

The overall prevalence of any AMD was 21.0%. No association was found between CEE plus progestin (odds ratio [OR], 0.91; 95% CI, 0.75-1.11) or CEE alone (OR, 0.98; 95% CI, 0.78-1.25) and early-stage AMD. CEE plus progestin was associated with a reduced risk of soft drusen (OR, 0.83; 95% CI, 0.68-1.00) after adjustment for covariates and with a reduced risk of neovascular AMD (OR, 0.29; 95% CI, 0.09-0.92).

“Our finding of a protective effect for neovascular AMD is consistent with a case-control study that found a protective effect for CEE use but did not evaluate unopposed versus combination therapy,” the authors wrote.

## Most Patients With Traumatic Choroidal Rupture Do Not Achieve 20/40 or Better VA

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In another *Archives of Ophthalmology* study, investigators found that most patients who have a traumatic choroidal rupture do not achieve a final visual acuity of  $\geq 20/40$ . They reported that poor visual outcome was

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most highly associated with a macular rupture and baseline visual acuity of <20/40. The formation of choroidal neovascularization (CNV) was most strongly associated with older age and macular choroidal rupture.

To determine predictors of CNV and visual outcome after traumatic choroidal rupture, the investigators conducted a retrospective review of patients with traumatic choroidal rupture diagnosed in the Retina Service, Massachusetts Eye and Ear Infirmary, Boston, between January 1993 and August 2001. Parametric and non-parametric statistical methods were used to evaluate visual prognosis, CNV and retinal detachment after traumatic choroidal rupture.

There were 111 cases identified and reviewed. Visual acuity changes were recorded in all of the cases; 38 (34%) of the 111 patients recovered driving vision (visual acuity 20/40). Rupture location was recorded in 107 cases. Recovery of driving vision was seen in 20 (59%) of 34 eyes with peripheral choroidal ruptures, 17 (22%) of 73 eyes with macular choroidal ruptures, 38 (38%) of 99 eyes without CNV, 1 (8%) of 12 eyes with CNV, 38 (40%) of 96 eyes without retinal detachment, and 1 (7%) of 15 eyes with retinal detachment.

According to the report, older age and location of rupture within the arcades were positively associated with CNV formation ( $P=.04$  and  $.03$ , respectively). Foveal location of rupture, multiple ruptures and poor baseline visual acuity were associated with failure to recover driving vision in univariate regression analyses. Rupture location and baseline visual acuity were independently associated with visual outcome in multivariate analysis. Of 12 patients diagnosed with CNV, five were not treated, four were treated with argon laser photocoagulation, one was treated with surgery, one was treated with argon laser photocoagulation followed by surgery, and one was treated with verteporfin photodynamic therapy (PDT) (Visudyne; Novartis, East Hanover, NJ).

## Lamina Puncture for CRVO Does Not Restore VA in Elderly

A pilot trial for lamina puncture in central retinal vein occlusion (CRVO) found that the procedure does not restore visual acuity in older patients.

Lamina puncture is a novel procedure used to create a perivascular opening within the optic nerve head by a transvitreal approach, the investigators wrote in *Archives of Ophthalmology*. They evaluated older CRVO

patients in a nonrandomized, consecutive, interventional case series. The patients were aged  $\geq 65$  years, had a visual acuity of  $\leq 20/200$  and were treated with vitrectomy and lamina puncture of the optic disc. Preoperative visual acuity, clinical examination results and fluorescein angiography results were compared with postoperative results.

Twenty patients (12 men and eight women), aged an average of 72 years, were enrolled. The mean duration of CRVO was 5.4 months; 14 eyes had nonischemic CRVO when first seen, and 6 had substantial ischemia, the investigators wrote. The mean preoperative visual acuity was in the counting fingers range, and the mean postoperative visual acuity was also in the counting fingers range. Five eyes had iris neovascularization, of which, four progressed to neovascular glaucoma. Also, preoperative ischemia seemed to predispose to neovascular complications.

## Prophylactic Retinopexy Failure in Fellow Eyes

Prophylactic retinopexy in fellow eyes without posterior detachment is not completely successful and may cause breaks to develop at the edge of treated areas during subsequent acute posterior vitreous detachment, according to an *Archives of Ophthalmology* report. The authors from Moorfields Eye Hospital in London said that patient education alone regarding the symptoms of retinal tear and detachment may be preferable to prophylactic retinopexy of the fellow eye in the absence of a posterior vitreous detachment.

To describe adverse sequelae of retinal prophylaxis in fellow eyes of patients with rhegmatogenous retinal detachment, the investigators reviewed records for 17 patients who had retinal breaks or detachment subsequent to prophylactic retinopexy applied to the fellow eye (without posterior vitreous detachment) at the time of primary rhegmatogenous retinal detachment surgery. They wrote that subsequent treatment included cryotherapeutic and laser retinopexy, scleral buckling and vitrectomy.

The 17 patients had a mean age of 49 years and 12 were men. Laser retinopexy alone was used in 6 cases. Sixteen (94%) developed retinal tears related to acute posterior vitreous detachment, of which eight (47%) were at the edge of retinopexy and eight (47%) were in the normal or untreated retina. Thirteen (76%) developed a retinal detachment, of which 11 (85%) did not

involve the fovea. Median visual acuity following treatment was 0.18 logMAR (6/9 Snellen equivalent).

## OCT Useful in Detecting Retinal Necrosis

Optical coherence tomography (OCT) allows the detection of full-thickness retinal necrosis in the acute phase and complete absence of retinal structure in the resolution phase, corresponding with the yellowish-white lesions seen in patients with acute retinal necrosis.

Researchers reporting in *Ocular Immunology and Inflammation* analyzed retinal findings in seven eyes with acute retinal necrosis and performed OCT. The OCT images depicted highly reflective areas in the inner layers of the retina in all seven cases, corresponding with the yellowish-white lesions of the retina in the acute phase. Disorganization of the retinal structure was also observed in these retinal lesions, especially in cases with severe inflammation. Subretinal changes including retinal exudate and/or fluid were observed in only one case. After regression of the yellowish-white lesions in the retina, a significant reduction in retinal thickness was observed on OCT.

### INDUSTRY AND BUSINESS AND NEWS

## Lumenis Invests in Exclusive, Worldwide License for New Ophthalmic Technology

Lumenis (Yokneam, Israel), a global developer, manufacturer and seller of laser and light-based devices for medical, aesthetic, ophthalmic, dental and veterinary applications, has received exclusive worldwide licensing rights for SRT, a new laser therapy for selectively treating retinal diseases. These rights include licenses issued to Lumenis by Medizinisches Laserzentrum Lübeck GmbH (Lübeck, Germany), Massachusetts General Hospital and Professor Reginald Birngruber, according to a news release.

SRT is a novel technology that selectively targets and confines the treatment to the retina pigment epithelium at the back of the retina. Since there is little heat generated, the surrounding photoreceptors are left undamaged and its normal function is sustained. Therefore, SRT represents a paradigm shift for retinal laser treatments with the potential to enhance sight preservation for patients

affected by several retinal diseases, according to a company news release.

According to Professor Birngruber, chairman of the Medizinisches Laserzentrum Lübeck, Germany, and visiting professor at Harvard Medical School. "The more challenging ophthalmic diseases are those that affect the retina and posterior pole. Treatable retinal conditions, such as DR and AMD, currently rely primarily on other solutions. Laser photocoagulation is the accepted standard of care for DR patients, while [PDT] is the current standard for treating AMD patients. Although both of these laser treatments reduce disease progression, they seldom restore or improve visual acuity. SRT, on the other hand, has the potential of doing both. This is a breakthrough for ophthalmology and sight preservation." For more information, please visit [www.lumenis.com](http://www.lumenis.com).

## Bascom Palmer Eye Institute Opens Country's Most Advanced Eye Care Center

Bascom Palmer Eye Institute (Palm Beach Gardens, Fla) has opened the most technologically advanced eye care center in the United States, located on a 7.4-acre campus in Palm Beach Gardens, according to a news release.

"This \$22 million expansion reaffirms Bascom Palmer Eye Institute's long-standing commitment to deliver the highest level of ophthalmologic care, research and education," said Carmen A. Puliafito, MD, MBA, chairman of Bascom Palmer Eye Institute, the world-renowned department of ophthalmology at the University of Miami Miller School of Medicine and the nation's top-ranked eye hospital.

With a uniquely comprehensive array of cutting-edge ophthalmologic technology at a single site, this campus supports a dramatic expansion in clinical care and research," added Puliafito. He noted that the academic ophthalmic center is a model for 21st century eye care centers and a magnet for the best and brightest eye care specialists.

The new campus, which triples the size of the institute's facilities in Palm Beach County, features the Maltz Center, a 40,000 square-foot patient care medical office building with >50 examination rooms for the treatment of all ophthalmic diseases and disorders. It houses centers for retinal and macular diseases, imaging, glaucoma, cornea, LASIK, aesthetics and pediatric ophthalmology. It also includes a center for low vision rehabilitation and an optical shop. Adjacent to the

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medical office building is the Frankino Pavilion at the Bascom Palmer Surgery Center. The 10,000 square-foot, state-of-the-art ambulatory surgery center now allows Bascom Palmer's physicians to perform retina, cataract, glaucoma, ophthalmic plastic and reconstructive surgeries on-site.

Yunhee Lee, MD, MPH, medical director and division chief of Bascom Palmer Eye Institute at Palm Beach Gardens, said the institute's \$4 million investment in surgical, diagnostic and patient care equipment at the new campus provides a host of treatment options for patients of all ages, while streamlining business and clinical practices. For example, with \$1.5 million in refractive lasers, the LASIK/refractive surgery suite features every major model of the latest laser equipment available in the market today, expanding customized treatment options.

To evaluate patients with *dry* AMD and other macular diseases, the institute has installed a digital fundus autofluorescence system that captures digital images of the retina and macula to detect the early signs of disease progression. This emerging technology is finding new applications in the field of macular disease, as retina physicians at Bascom Palmer continue their leading role in the diagnosis and treatment of age-related macular degeneration.

To support its world-renowned medical research, training programs and academic conferences, the LASIK and Vision Correction Center's surgical suite incorporates an observation area and 50-seat conference theater designed for patient and physician education. For educational purposes, surgical procedures can also be simulcast to academic centers worldwide. In the adjacent ambulatory surgery center, three operating rooms house the latest in ophthalmic surgical instrumentation, and 14 presurgical and postoperative recovery stations are available for patients.

The campus significantly expands space for Bascom Palmer clinical studies, including full-time specialists who will oversee patient care and research in conditions and diseases of the retina. The institute's retina specialists have been involved in every major clinical trial for the treatment of the wet form of macular degeneration for the last decade. Already underway is the HORIZON trial, a national study intended to learn the long-term safety and efficacy of ranibizumab (Lucentis; Genentech, San Francisco), a drug approved June 30 by the FDA for treatment of neovascular AMD, a potential blinding condition which affects 8 million Americans.

For further information about Bascom Palmer Eye Institute, please visit [www.bascompalmer.org](http://www.bascompalmer.org)

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## Macusight Announces FDA Acceptance of IND for Novel Ophthalmic Drug Candidate

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Macusight (Union City, Calif), a developer of innovative therapeutics for the treatment of severe ocular diseases and conditions, announced that the FDA has accepted the company's investigational new drug (IND) application for its proprietary formulation of sirolimus (rapamycin). The IND covers the compound's development as a treatment for neovascular AMD and diabetic macular edema (DME). Macusight intends to initiate a phase 1 clinical trial of its lead product candidate in DME during this year's third quarter and a phase 1 trial in neovascular AMD during the fourth quarter.

"We are pleased with the rapid progress of our ongoing efforts to develop our proprietary sirolimus drug candidate for the treatment of serious ocular diseases and conditions such as [neovascular] AMD and DME," said David A. Weber, PhD, Macusight's president and chief executive officer. "The therapeutic potential for this product is very exciting and we are eager to initiate our phase 1 clinical trials."

Sirolimus, originally known as rapamycin, is a highly-potent, broad-acting compound that has demonstrated the ability to combat disease through multiple mechanisms of action including immunosuppressive, antiangiogenic, antimigratory, antiproliferative, antifibrotic and antipermeability activity. Based on the versatility associated with these multiple mechanisms of action, Macusight believes that its sirolimus product may serve as a potentially highly efficacious therapeutic for a wide range of ocular diseases and conditions.

"Sirolimus is a very interesting ocular drug candidate due to the fact that this broadly active compound's mechanisms of action, not unlike steroids, are relevant to the treatment of proliferative and hyperpermeability linked diseases such as [neovascular] AMD and [DR]," said Mark Blumenkranz, MD, chairman of Macusight's scientific advisory board and professor and chairman of the department of ophthalmology, Stanford University School of Medicine. Dr. Blumenkranz is also a member of the RETINA TODAY editorial board. "Additionally, the compound directly inhibits the mammalian target of rapamycin, directly impacting immunomodulation as well as proliferation, survival, mobility and angiogenesis. As a result, we believe that sirolimus may have great potential as a next-generation agent for several severe ocular diseases, not only as a front-line therapy of active disease but prophylaxis as well."

To date, Macusight has compiled preclinical data that

demonstrates sirolimus' ability to inhibit CNV in both mice and rats. For more information, please visit [www.macusight.com](http://www.macusight.com)

## Ophthalmic Imaging Systems, IVN Partnership

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Ophthalmic Imaging Systems (Sacramento, Calif), a leading provider of ophthalmic digital imaging systems, announced a new partnership with a division of the International Physician Networks (IPN) and Ameri-source-bergen Specialty Group, the International Vision Network (IVN), the only specialty group purchasing program for ophthalmologists' offices and ambulatory surgery centers, according to the company.

Under the terms of the agreement, Ophthalmic Imaging Systems will serve as the exclusive vendor to IVN for new digital imaging system units used in the ophthalmic setting, including fundus cameras and slit lamps.

IVN will endorse and offer special discounts on Ophthalmic Imaging Systems' products to IVN members. IVN's membership includes 250 retina specialty practices numbering >1,000 retina surgeons. IVN's Ambulatory Surgery Center Membership includes more than 60 eye surgery centers representing >100,000 eye surgical procedures annually. For more information, please visit [www.oisi.com](http://www.oisi.com).

## OSI, Pfizer Announce Phase 4 Maintenance Trial

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OSI Pharmaceuticals (New York, NY) and Pfizer (New York, NY) have initiated the LEVEL trial (Evaluation of Efficacy and Safety in Maintaining Visual Acuity with Sequential Treatment of Neovascular AMD), a phase 4 trial that will explore the safety and efficacy of pegaptanib sodium injection (Macugen) as a maintenance therapy for patients who have received prior neovascular AMD treatment and experienced improvement in macular disease.

The 54-week trial will evaluate up to 1,000 patients at 100 sites across the country. Neovascular AMD is a chronic, progressive disease that may require ongoing management. Nearly 70,000 patients have already been treated with pegaptanib, which offers proven efficacy and safety for up to 2 years in the treatment of neovascular AMD with 6-week dosing. Safety may be an important consideration when choosing a maintenance therapy. According to retrospective Medicare data presented at ARVO, patients with neovascular AMD are typically older, with

significantly more comorbid conditions such as hypertension, diabetes, lipid disorders, stroke and myocardial infarction than those who do not have neovascular AMD.

"Armed with a growing number of treatment options, we should explore new regimens that may be capable of providing beneficial patient outcomes while addressing long-term safety and dosing considerations," said Thomas R. Friberg, MD, MS, professor of ophthalmology and bio-engineering at the University of Pittsburgh Medical Center and a lead investigator in the LEVEL trial. "For example, clinical data suggest that a nonselective anti-VEGF-A therapy can improve vision in a significant portion of patients and that this improvement may stabilize after a few injections. It makes sense to study whether these gains can also be maintained using a selective anti-VEGF therapy." Dr. Friberg is also a member of the RETINA TODAY editorial board.

For more information, please visit [www.macugen.com](http://www.macugen.com).

## Athenagen Develops Eye Drop Therapy for AMD

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Athenagen (San Francisco) announced that it is testing ATG003, a topical eye drop therapy for AMD.

The therapy — a proprietary topical formulation of mecamlamine that has shown efficacy in animal models and is a possible alternative to current therapies for AMD — is being tested in a randomized, placebo-controlled, ascending dose, phase 1 clinical trial designed to evaluate ocular tolerability and safety for ≤14 days. This study represents the first human study of an eye drop antiangiogenic therapy for AMD. ATG003 is a novel antiangiogenic agent that inhibits endothelial nicotinic acetylcholine receptors and has been shown to decrease angiogenesis as well as vascular permeability.

"Complementing our promising preclinical efficacy studies are robust data demonstrating excellent penetration of the drug to the back of the eye," said M. (Ken) Kengatharan, PhD, cofounder and vice president of preclinical research and development at Athenagen. "This proprietary eye drop formulation of mecamlamine enables delivery of drug to the retina and choroid with very little reaching the systemic blood circulation."

"Given the prevalence of AMD and the invasive nature of current treatments, a topical noninvasive eye drop for treating this disease would be . . . welcome," said Michael Marmor, MD, professor of ophthalmology, Stanford University School of Medicine. ■