

CREST STUDY SHOWS THAT CAROTENOIDS IMPROVE HEALTHY VISION, CONTRAST SENSITIVITY

Supplemental carotenoids can improve already healthy vision, according to a study by the Macular Pigment Research Group at the Nutrition Research Centre Ireland, part of the School of Health Sciences at Waterford Institute of Technology, Waterford. In the Central Retinal Enrichment Supplementation Trials (CREST), John M. Nolan, PhD, and colleagues investigated the potential benefits of lutein, zeaxanthin, and meso-zeaxanthin supplementation in individuals whose eyes lack sufficient concentrations of macular pigment (MP). Notably, this study focused on people with strong eyesight instead of those who need corrective action, according to a MacuHealth press release.

CREST was a parallel, double-blind, placebo-controlled, block-randomized study that enrolled 105 subjects. Over a 12-month period, 53 subjects received a daily formula of naturally occurring carotenoids (10 g lutein, 10 g meso-zeaxanthin, 2 g zeaxanthin), and 52 patients received a placebo. Observations were recorded at baseline and at 3, 6, and 12 months.

Researchers calculated changes in mean contrast sensitivity across various spatial frequencies, with six cycles per degree (cpd) constituting the primary outcome measure between the two groups. The active group demonstrated a statistically significant improvement from baseline at both 6 ($P = .002$) and 1.2 ($P = .004$) cpd compared to the placebo. This improvement coincided with an observed increase in MP ($P = .002$ at 6 cpd). No statistically significant relationships, however, were found between changes in lutein concentration and changes in contrast sensitivity at any recorded spatial frequency.

The authors concluded that supplementation of macular carotenoids (lutein, zeaxanthin, and meso-zeaxanthin) can increase MP and significantly enhance visual function and contrast sensitivity. This improvement may be particularly beneficial for reducing eye strain while reading as well as for improving the detection of moving and nonmoving objects while driving or playing sports, Dr. Nolan explained in the press release. *The study was funded by the European Research Council.*

FDA Accepts 510(k) Premarket Notification Filing for the Xen Glaucoma Treatment System

Allergan announced that the 510(k) premarket notification application for the Xen Glaucoma Treatment System, consisting of the Xen45 Gel Stent and the Xen Injector, has been accepted for filing by the FDA. Xen45 is a minimally invasive, implantable, cross-linked gelatin shunt used to reduce IOP associated with refractory glaucoma. Xen45 is CE Marked in the European Union, where it is indicated for the reduction of IOP in patients with primary open-angle

glaucoma when previous medical treatments have failed, the company reports. The device is also licensed for use in Canada, Switzerland, and Turkey.

NeurAegis Presents Potential Glaucoma Treatment

Michel Baudry, PhD, and his team at Western University of Health Sciences identified a selective calpain-2 inhibitor, NA 101, that may be a promising treatment for acute glaucoma, according to a NeurAegis press release. The enzyme calpain is neuroprotective in one isoform (calpain-1) and

neurodegenerative in another (calpain-2). Dr. Baudry's team used a mouse model to test the efficacy of the inhibitor as a neuroprotective agent. After generating an increase in IOP for 2 hours to activate calpain-2, they injected NA 101 into the mice. As a result, 75% of the retinal ganglion cells that would have otherwise died were protected, according to the release. Although calpain has long been associated with long-term potentiation, its importance in neuron function was not particularly appreciated until now, reports NeurAegis, a newly formed company based around this discovery. The company hopes that a new treatment for acute glaucoma will be available in the next few years.

Gulden Ophthalmics Introduces Medication Compliance System

The ComplyNow Medication Compliance System, currently in development by Gulden Ophthalmics, is wearable technology designed to help patients remember to take medications. The device, which can be worn as a necklace pendant, key fob, or wristband, offers reminders and records when a patient takes or misses a dose.

Physicians can then view a patient's entire compliance history and take action as needed. The de-identified patient information is automatically uploaded to an online database (courtesy of EyeCare Registry), which can be accessed by researchers. Gulden anticipates that final production units will be available in January 2017 for approximately \$30.

Nicox to Transfer Commercial Operations to Pan-European Ophthalmic Specialty Pharmaceutical Company

Nicox has announced that it will transfer its European and international commercial operations to a newly founded private company focused on the commercialization of a portfolio of ophthalmic products in Europe, according to a Nicox press release. The new company is currently being structured by GHQ Capital and will combine Nicox's existing European and international commercial infrastructure and portfolio, including some products in late-stage development for Europe only. All rights to Nicox's unencumbered research and development pipeline programs, including AC-170 and rights under the latanoprostene bunod agreement with Bausch + Lomb, remain entirely with Nicox.

This transaction is the result of Nicox's previously

announced review of strategic opportunities for its European and international commercial operations, and it is a key step in refocusing the company's resources on its research and development pipeline in ophthalmology, including AC-170 for allergic conjunctivitis (FDA Prescription Drug User Fee Act date October 18, 2016), NCX 4251 for blepharitis, NCX 470 for lowering IOP in patients with glaucoma and ocular hypertension, and the new generation of nitric oxide stand-alone donors in glaucoma, the company explained. Nicox will continue to support Bausch + Lomb in advancing the nitric oxide-donating prostaglandin F₂- α analog latanoprostene bunod (FDA Prescription Drug User Fee Act date July 21, 2016).

The commercial organization covered by this transaction currently markets more than 25 products in the top five European markets and through its distributors in more than 40 other markets, according to the press release. These assets will all be transferred to the new company. The transaction values Nicox's European and International operations portfolio and late-stage European development programs at up to €26 million. Under the terms of the transaction, Nicox will assign related product and trademark rights to the new company (or corresponding agreements with third parties), including rights to its commercial portfolio of ophthalmology products and rights to some development candidates in Europe.

In exchange for these assets, and upon closing of the transaction, Nicox will receive €9 million in cash and a combination of ordinary shares and interest-bearing loan notes valued at an aggregate of €12 million. Nicox will also gain the right to receive up to €5 million in additional loan notes on the achievement by the new company of agreed business and commercial milestones.

Under the terms of the transaction, Nicox will be responsible for completing, at its own cost, the development and regulatory approval in Europe of product candidates transferred to the new company, the press release noted. Nicox is eligible to receive reimbursement of some costs upon achievement of regulatory and commercial milestones associated with these product candidates. Nicox will provide a number of transitional services to the new company.

Inotek Pharmaceuticals Initiates Phase 2 Dose-Ranging Trial of Trabodenoson and Latanoprost

Inotek Pharmaceuticals initiated a phase 2 dose-ranging trial of a fixed-dose combination of trabodenoson and latanoprost. According to an Inotek news release, trabodenoson is a highly selective adenosine A₁ mimetic that has been observed in phase 2 clinical trials to reduce

A NEW OPTION FOR UVEITIS

Adalimumab, a rheumatology drug, offers hope to patients with this damaging inflammatory eye disease.

BY AGUSTIN L. GONZALEZ, OD



There is no doubt that 2016 will be remembered as a year of innovations in pharmaceuticals for eye care, and there is also no doubt that patients will be the recipients of the benefits of these innovations. With the recent approval of adalimumab (Humira; AbbVie) for the treatment of uveitis, eye care providers now have an expanded therapeutic armamentarium for the management of this damaging inflammatory disease.

The FDA approved adalimumab in June for ophthalmic use in the treatment of noninfectious intermediate and posterior uveitis and panuveitis. A representative of the class of pharmaceutical agents targeting tumor necrosis factor α (TNF- α), this drug has a long, safe history in the treatment of several types of rheumatic

diseases.^{1,2} Compared with other anti-TNF- α treatments, adalimumab has been noted to generate fewer adverse or allergic events, possibly because of the biochemical structure of the molecule.³ The additional indication in the field of ophthalmology for the treatment of uveitis follows other indications added in recent years for intestinal Behçet disease and severe ulcerative colitis.⁴

TNF- α is a pleiotropic or single-gene expression, multiple-cell origin cytokine that affects multiple systems and plays a leading role in the pathogenesis of uveitis. Interleukin 10 (IL-10) is an anti-inflammatory cytokine expressed by CD4+ T cells as a consequence of anti-TNF- α treatment that, together with down-regulation of macrophages, has been posited as the mechanism of action of many TNF- α -blocking drugs. It is thought that CD4+ T cell expression of IL-10 leads to the resolution of uveitis with anti-TNF- α treatment.^{1-3,5}

IOP, and latanoprost is a prostaglandin analogue and the most commonly used drug for lowering IOP.

"Trabodenoson is designed to restore the eye's natural pressure by increasing aqueous humor outflow via the trabecular meshwork, the primary outflow apparatus of the eye and a site of pathology in glaucoma. Existing therapies, including prostaglandin analogues, primarily regulate eye pressure through other mechanisms such as the uveoscleral or secondary pathway. We believe that a fixed-dose combination of trabodenoson with latanoprost has the potential to provide patients and physicians with a novel treatment option that offers the convenience of a single daily drop, with two complementary eye pressure lowering mechanisms, and an optimized safety and efficacy profile," said Rudolf Baumgartner, MD, chief medical officer of Inotek, in the news release.

The randomized, double-masked, phase 2, dose-ranging trial will assess the overall benefit/risk profile of binocular topical application of different daily doses of trabodenoson (3.0% and 6.0%) when combined with latanoprost (0.005% or 0.0025%) in patients with ocular hypertension

or primary open-angle glaucoma. Three treatment combinations of trabodenoson and latanoprost will be investigated as well as two separate concentrations of latanoprost alone. The trial will enroll approximately 165 patients with an IOP greater than or equal to 25 mm Hg and less than or equal to 34 mm Hg. Following a placebo run-in period, treatment will be administered to both eyes for a total of 8 weeks. Each subject will be assigned 4 weeks of morning and 4 weeks of evening dosing in a masked manner.

For more information, visit www.clinicaltrials.gov/ct2/show/NCT02829996.

Latanoprostene Bunod Ophthalmic Solution 0.024% Phase 3 Study Results Published

The results of a phase 3 study for latanoprostene bunod (LBN) ophthalmic solution 0.024% (Bausch + Lomb) were published in the *American Journal of Ophthalmology*.¹ Nicox licensed LBN 0.024%, an IOP-lowering single-agent

Traditional Indications

Adalimumab has long been approved for use in adults with moderate to severe rheumatoid arthritis, severe active ankylosing spondylitis, moderate to severe chronic plaque psoriasis, and active or progressive psoriatic arthritis. The drug is also used in moderately to severely active Crohn disease, moderately to severely active ulcerative colitis, and moderately to severely active hidradenitis suppurativa. Indications in the pediatric population include active enthesitis-related arthritis, severe chronic plaque psoriasis, severely active Crohn disease, and active polyarticular juvenile idiopathic arthritis.⁶

Study Results

The regulatory approval decision was based on the results of two phase 3 studies, VISUAL-I and VISUAL-II. Both studies were double masked and placebo controlled, and both enrolled adult patients with active and controlled noninfectious intermediate and posterior uveitis and panuveitis. Investigators found that patients who were treated with adalimumab had a statistically significantly lower risk for treatment failure than those receiving placebo. Treatment failure was defined as an increase

in anterior chamber cells or vitreous haze, new chorio-retinal or vascular lesions, or a decrease in visual acuity.^{1,7}

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eye drop dosed once daily for patients with open-angle glaucoma or ocular hypertension, to Bausch + Lomb in March 2010.

The primary objective of the randomized, multicenter, noninferiority study known as LUNAR was to demonstrate noninferiority to timolol, while the secondary objective was to demonstrate superiority. Of 387 enrolled patients, 259 used LBN once per day, and the rest used timolol twice per day. IOP was measured at nine time points over a 3-month period.

Mean IOP was significantly lower in the LBN 0.024% group than in the timolol 0.05% group at all but one time point. The reduction from baseline ranged from 29.1% to 32.1% in the LBN 0.024% group and from 25.2% to 28.7% in the timolol group. The LBN group exhibited a slightly higher number of adverse events, including conjunctival hyperemia, eye irritation, and eye pain. The study demonstrated that LBN 0.024% administered once daily in the evening was not only noninferior to timolol maleate 0.5% dosed twice daily in subjects with open-angle glaucoma or ocular hypertension over 3 months of treatment but that it also provided a

significantly greater IOP reduction ($P \leq 0.025$) at all but the earliest time point evaluated.

A second, similarly designed study, published in the May issue of *Ophthalmology*,² also demonstrated the efficacy of LBN 0.024% for IOP lowering. In this randomized, controlled, multicenter, double-masked, parallel-group, noninferiority clinical study called APOLLO, the primary efficacy endpoint was IOP in the study eye measured at the same nine assessment time points as in LUNAR. Results showed that the mean IOP in the study eye was significantly lower in the LBN 0.024% group (range, 17.8-18.7 mm Hg) than in the timolol 0.5% group (range, 19.1-19.8 mm Hg) at all nine efficacy time points assessed. In July 2015, Bausch + Lomb submitted a New Drug Application to the FDA, which set an action date of July 21, 2016. ■

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