PETITION TO
THE U.S. FOOD & DRUG
ADMINISTRATION

Petitioner: Resveratrol Partners LLC
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1. Introductory letter to the commissioner

Date

By certified mail, return receipt requested

Margaret Hamburg MD, Commissioner
U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dockets Management Branch
Food and Drug Administration, Room 1061
5630 Fishers Lane
Rockville, MD 20852


Dear Commissioner Hamburg:

The subject of this petition is time-sensitive. A timely response from your agency is necessary as it is estimated ~7500 elderly patients will suffer permanent vision loss during the 90-day response period by your agency.


This petition is written in context of the FDA’s position to promote innovation in medicine and to work in a timely manner regarding any irreversible threat to health that requires immediate agency action.
This petition is being filed to request conditional approval of oral Longevinex® dietary supplement capsules for treatment of elderly patients with wet (neovascular) macular degeneration who have failed treatment with injectable anti-angiogenesis drugs bevacizumab (Avastin) and ranibizumab (Lucentis).

This unusual petition is being submitted because all treatment options have been exhausted and these patients, most whom are in their eighth decade of life, face permanent vision loss unless timely and effective treatment is rendered.

It is estimated that 1 in 6 patients treated with bevacizumab (Avastin) and ranibizumab (Lucentis) progress to registered blindness. As miraculous as these drugs are, an estimated 30,000 elderly patients per year (80-100 patients per day) fail to be helped by injectable monoclonal antibody vascular endothelial growth factor (anti-VEGF) blockers.

While anti–VEGF monoclonal antibodies have fundamentally altered the clinical management of choroidal neovascularization (wet macular degeneration), as these drugs were the first to reliably improve vision, even if only for 30-45 days between injections, a noted authority has stated that “anti–VEGF-A antibody therapy is not a panacea, as only one third of patients recover driving vision and one sixth progress to registered blindness.”

Preliminary cases treated with Longevinex® have rapidly responded to this oral medication with some dramatic unexpected remissions and measured restoration of functional vision. No side effects have been reported among these limited cases. Sixteen of the first seventeen cases treated responded positively to Longevinex (this was not a controlled trial, it was an accumulation of individual cases). Nor have serious side effects been reported.

1 Ambati, J. Age-Related Macular Degeneration and the Other Double Helix, Invest Ophthalmology Vis Sci. 2011; 52: 2166–2169

reported among a broader group of thousands of adults who have taken this product over a period of 8 years for general health promotion.

Resveratrol Partners LLC fully recognizes the conventional way to proceed with a nutriceutical intended to treat or cure any disease is to file an investigational new drug application and proceed with a double-blind placebo-controlled study of adequate duration. However, such a study will (a) delay timely treatment for thousands of patients and (b) would be unethical as it would force patients who are going blind to take an inactive placebo and (c) would be too costly for such a small patient population. (It is estimated a 1-year 1332-case study, similar to the study used to approve Lucentis, would cost over $4.5 million.)

In the proposed trial, no placebos would be employed in agreement with the World Medical Association Declaration of Helsinki recommendations which stipulate that “In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic methods.”

Resveratrol Partners LLC maintains that bevacizumab (Avastin) and ranibizumab (Lucentis) should serve as the control group, which is a much more difficult comparison standard to demonstrate efficacy than comparison against placebo.

The sponsor/applicant appeals to the FDA to accept this petition in place of a New Drug Application, which is beyond the capability of such a small business entity to fund. Furthermore, a NDA would delay approval and condemn many thousands to permanent loss of sight.

Because of these unusual circumstances, Resveratrol Partners LLC petitions the Food & Drug Administration to allow it to proceed with use of

its unique oral nutriceutical capsules for treatment of these cases as long as it can be shown with reasonable certainty that no patients will be harmed. Animal dosing and human and animal toxicity studies have been done and are presented in the appendix herein.

Longevinex® is a dietary supplement manufactured in a GMP establishment in the U.S. It has been marketed in the U.S. since 2004 and sold to thousands of patients with no reported serious adverse reactions. Reported transient or minor adverse reactions associated with this nutriceutical are listed with commentary in this report. A printed product insert warns clinicians and consumers of potential drug interactions or other adverse effects.

The sponsor/applicant makes the FDA aware that the ingredients in its product address the known reason why anti-VEGF monoclonal antibodies fail.

The study would recruit patients via publicity who fail to respond after six (6) Avastin/Lucentis treatments, who then would contact their eye physician to enroll them in the study.

The treatment center would agree to comply with the study protocol and confirm it has the necessary equipment to perform required tests.

Because the sponsor/applicant is a small business entity, it is not in a financial position to pay investigators a typical $3000 per patient fee to conduct tests and tabulate and submit data. Investigators would be participating voluntarily.

The sponsor of the study applies to the FDA as a small business entity and applies for user fees to be waived.

The number of subjects enrolled in the study would initially be limited to 250 and expand as the sponsor is capable and FDA gives a go-ahead.

The patients would qualify for the study if having undergone at least six (6) consecutive unsuccessful Avastin/Lucentis injections.

Patients would be examined at baseline entry into the study, at 6 weeks, and 6 months. Because these patients face imminent permanent loss of
vision, long-term data would not be deemed to be as important as intervention that would rapidly avert permanent vision loss. The length of the trial can be extended based upon 6-month data.

Adverse reactions, serious or otherwise, would be reported on a standardized form and any serious adverse reactions would be immediately reported to the FDA.

To repeat, public health is at grave risk. A timely response from your agency is necessary as it is estimated ~7500 elderly patients will suffer permanent vision loss during the 90-day response period.
2. Actions requested

The applicant/petitioner pleads for the following:

- Waiver of requirement to submit an application as an investigational new drug in light of its inherent delay in delivering a potential cure to otherwise hopeless patients who face permanent loss of vision.

- Conditional approval to proceed with a human clinical trial based upon provision of toxicity and safety data, under the dictum “first do no harm.”

- Waiver of the traditional demand to compare its nutriceutical product against an inactive placebo. Placebo users would likely face permanent and inevitable loss of vision. A placebo-controlled trial would be unethical in these circumstances. The World Medical Association Declaration of Helsinki recommendations stipulate that “In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic methods.”

- Waiver of user fees and designation as a small business entity as the cost to perform a 1-year double-blind placebo-controlled study is excessive (estimated at $4.5 million) in light of such a small patient population, estimated at 30,000 per year who fail anti-VEGF treatment.

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3. Waiver for user fees and designation as a small business entity

Under section 736(d)(1)(B) of the FD & C Act, the FDA makes the following inquiries regarding qualification for waiver of user fees and designation as a small business entity.

- **Is the drug product a significant improvement (or does it have the potential to be a significant improvement if the drug product is not yet approved) compared to other marketed products, including other dosage forms or routes of administration and non-drug products or therapies?**

  Reply: there are no current approved or off-label therapies for patients who fail monoclonal antibody/anti-VEGF treatment for wet macular degeneration.

- **Are there treatment alternatives? The existence of alternatives would weigh against a determination that a product is necessary to protect the public health.**

  Reply: Again, there are no alternative treatments. Patients refractory to treatment face repeated but ineffective re-treatment via needle injection to the eye.

- **Does the drug product demonstrate an increased effectiveness in the treatment, prevention, or diagnosis of disease?**

  Reply: the nutraceutical has demonstrated in a small number of cases that it can resolve cases of wet macular degeneration in a timely manner. The petition pleads for permission to proceed with a human clinical trial without the delay and cost of an Investigational New Drug Application.
• Does it eliminate or substantially reduce a treatment-limiting drug reaction?

  Reply: Current treatment subjects patients to an invasive needle injection directly into the eye with the risk of hemorrhage or infection.

• Does the drug product enhance patient adherence to treatment?

  Reply: the oral nutriceutical can be used concomitantly with injectable anti-VEGF treatment. The combination of these two therapies may improve visual results and patient attendance.

• Has the drug product shown potential evidence of safety and effectiveness for a new or underserved subpopulation?

  Reply: the nutriceutical has undergone animal toxicity testing and animal and human kidney toxicity testing as well as dosing studies in animals. It has been used without report of serious side effects for 8 years as a dietary supplement.

• Is the drug product intended for the treatment of a serious or life-threatening condition?

  Reply: patients with wet macular degeneration refractory to anti-VEGF treatment face permanent loss of sight. One in six will progress to registered blindness and only one-third of patients recover driving vision.

• Does the drug product address unmet medical needs or demonstrate the potential to do so?

  Reply: the nutriceutical meets an unmet need and addresses the biological causes of why anti-VEGF treatment fails.
If the product is approved, is it available to the public? There is no benefit to the public health if a product is not made available to the public.

Reply: the product is already directly available to the public as a dietary supplement for nutritional support of eye health. But to gain the medico-legal status as an approved therapy that may qualify for Medicare reimbursement, it will need to achieve approval as a drug. According to a recent survey, 46% of retirees live solely off the income of a Social Security check and may not be able to afford the out-of-pocket costs to purchase this nutriceutical. Most of the patients with wet macular degeneration are in their 80s.

Under section 736(d)(1)(B) of the Act, an applicant may qualify for a waiver of or reduction in application, product, and/or establishment fees when the assessment of the fees would present a significant barrier to innovation because of limited resources available to the applicant or other circumstances. Under this provision, FDA may grant a waiver of or reduction in user fees if:

The product or other products or technologies under development by the applicant are innovative; and the fee(s) would be a significant barrier to the applicant’s ability to develop, manufacture, or market innovative products or to pursue innovative technology.

Does the drug product or technology demonstrate advanced "breakthrough" research, new, progressive methods, and/or forward thinking in the treatment or diagnosis of disease, or does it have the potential to be at the forefront of new medical technology?

Reply: the nutriceutical has been shown by NIH researchers to down-regulate microRNA20b which controls angiogenesis via VEGF. It down-regulates microRNA20b -1366-fold versus -189-fold by plain resveratrol (6-fold greater anti-VEGF effect.)
• Does the drug product or technology introduce a unique or superior method for diagnosing, curing, mitigating, treating, or preventing a disease, or for affecting a structure or function of the body?

   Reply: the nutriceutical employs small molecule synergism and broad epigenetic influence, greater than the anticipated additive sum of its parts.

FDA will consider the total annual revenue of an applicant and its affiliates in determining whether the applicant has limited financial resources. Ordinarily, beginning with fees assessed for FY 2011, the Agency expects to determine that an applicant with financial resources, including the financial resources of affiliates, of less than $20 million has limited resources for user fee purposes.

Under section 736(d)(1)(D) of the Act, an applicant is eligible for a waiver of the application fee if the applicant is a small business submitting its first human drug application to the Agency for review and does not have another product approved under a human drug application and introduced or delivered for introduction into interstate commerce. An applicant is eligible for a small business waiver when:

• The applicant employs fewer than 500 employees, including employees of affiliates;
• The applicant does not have a drug product that has been approved under a human drug application and introduced or delivered for introduction into interstate commerce; and
• The applicant, including its affiliates, is submitting its first human drug application.

   Reply: The applicant/petitioner employs 4 workers and has annual gross revenues under $2 million. The applicant/petitioner does not currently have an approved human drug application.
4. Statement of grounds

There are no existing therapies for treatment of patients with wet macular degeneration who have failed anti-VEGF treatment by direct injection of monoclonal antibodies into the eye. These patients face permanent and inevitable loss of vision.

The FDA has chosen to approve monoclonal antibody injections for wet macular degeneration based upon pooled data on the percentage of patients who maintain their sight (cessation of progressive vision loss) and their aggregate average gain in visual acuity as measured by the number of letters the patient can read on a standard visual acuity chart following treatment.

However, this is a skewed way of declaring the current drugs are effective. If at baseline the patient has 20/200 visual acuity or 20/400 visual acuity (legal blindness in the affected eye), which is not sufficient to retain a driver’s license, and the anti-VEGF drug maintains that person’s vision (it doesn’t worsen), the treatment has not improved the patient’s functional vision. If a more functional standard were used, only about one-third of patients experience a gain in visual acuity and two-thirds fail to improve. (See FDA press release below.)

FDA NEWS RELEASE
FOR IMMEDIATE RELEASE
P06-94
June 30, 2006

Accessed at
http://www.fda.gov/newsevents/newsroom/pressannouncements/2006/ucm108685.htm

FDA Approves New Biologic Treatment for Wet Age-Related Macular Degeneration

The Food and Drug Administration (FDA) today approved Lucentis (ranibizumab injection) for the treatment of patients with neovascular (wet) age-related macular degeneration (AMD). Lucentis is the first treatment which, when dosed monthly,
can maintain the vision of more than 90 percent of patients with this type of AMD. Lucentis is a new molecular entity (NME), meaning it contains an active substance that has never before been approved for marketing in any form in the United States. Lucentis will be the first FDA-approved product to provide prescription information in the new format for prescription drug package inserts, to provide professionals and consumers clear and concise prescription information.

"This approval is of great importance for the 155,000 Americans who are diagnosed each year with AMD, a common cause of severe and irreversible vision loss in older adults," said Dr. Andrew von Eschenbach, Acting Commissioner of Food and Drugs. "At a time when our elderly population is rapidly increasing, this product preserves quality of life for those affected by this disease, helping them to regain the ability to participate in everyday activities such as reading and driving."

AMD, a retinal disease causing severe and irreversible vision loss, is a major cause of blindness in individuals older than 55 years. Untreated, the majority of eyes affected with wet AMD may become functionally impaired. Wet AMD, which accounts for 10 percent of all AMD, is responsible for 80 percent of the associated vision loss.

The vision loss in wet AMD is caused by the growth of abnormal leaky blood vessels that eventually damage the area of the eye responsible for central vision. Lucentis is designed to block new blood vessel growth and leakiness, which ultimately lead to disease progression and such vision loss.

Lucentis, a biologic product, administered by injection into the eye, was shown to be safe and clinically effective in three multicenter, randomized studies of patients representative of the population usually affected with AMD. In clinical trials, nearly 95 percent of the participants who received a monthly injection maintained their vision at 12 months compared to approximately 60 percent of patients who received the control treatment.

Approximately one-third of patients in these trials had improved vision at 12 months. In a single study carried out for 24 months, these findings have been maintained with continued monthly dosing. The most commonly reported adverse events included conjunctival hemorrhage, eye pain, floaters, increased eye pressure and inflammation of the eye. Serious adverse events were rare and often related to the injection procedure including endophthalmitis (severe inflammation of the
interior of the eye), intraocular inflammation, retinal detachment, retinal tear, increased eye pressure and traumatic cataract.

Page Last Updated: 06/18/2009
5. **Longevinex® addresses known mechanism of failure of monoclonal antibody anti-VEGF drugs**

The mechanism by which anti-VEGF therapy fails has been identified.

A. A significant increase of macrophage infiltration in choroidal neovascular membrane is reported after anti-VEGF therapy.

B. Infiltrating macrophages in the choroidal neovascular membrane are capable of expressing pro-angiogenic factors such as vascular endothelial growth factor (VEGF).\(^5\) Krüppel-like factor 4 (KLF4) is a critical regulator of macrophage polarization. Macrophage KLF4 expression is robustly induced in M2 macrophages and is strongly reduced in M1 macrophages.

The Kruppel-like factor 2 and 4 (KLF2 KLF4)) transcription factors act as critical regulators of vascular endothelial homeostasis.\(^6\) Resveratrol induces expression of KLF4.\(^7\)

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The mechanism by which anti-VEGF therapy fails has been identified.\textsuperscript{8}

1. A significant increase of macrophage infiltration in choroidal neovascular membrane is reported after anti-VEGF therapy.

2. Infiltrating macrophages in the choroidal neovascular membrane are capable of expressing pro-angiogenic factors such as vascular endothelial growth factor (VEGF).

3. Krüppel-like factor 4 (KLF4) as a critical regulator of macrophage polarization. Macrophage KLF4 expression was robustly induced in M2 macrophages and strongly reduced in M1 macrophages.\textsuperscript{9}

The Krüppel-like factor 2 and 4 (KLF2 KLF4)) transcription factors act as critical regulators of vascular endothelial homeostasis. Resveratrol induces expression of KLF4.\textsuperscript{10}

\begin{footnotesize}
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\item \textsuperscript{8} Cao X, Macrophage polarization in the maculae of age-related macular degeneration: A pilot study. Pathology International 2011 Sep; 61(9):528-35.
\end{itemize}
\end{footnotesize}
An unexpected and troubling report emanating from Scripps Research Institute\(^\text{11}\) reveals that anti-VEGF drugs may be problematic long-term. The Scripps Research Institute investigators found that animals bred without the ability to produce VEGF lost blood supply to the retina, resulting in severe vision loss. Since VEGF is part of the wound healing response, the anti-VEGF treated eye may never heal properly and require perpetual treatment. A report published by Science Daily said anti-VEGF drugs are “considered prohibitively expensive and invasive.”\(^\text{12}\) The Scrippss researchers called for microRNA testing of drugs used to treat wet macular degeneration, something that Longevinex® has already undergone.


Targeted deletion of Vegfa in adult mice induces vision loss.

Kurihara T, Westenskow PD, Bravo S, Aguilar E, Friedlander M.

Abstract

Current therapies directed at controlling vascular abnormalities in cancers and neovascular eye diseases target VEGF and can slow the progression of these diseases. While the critical role of VEGF in development has been well described, the function of locally synthesized VEGF in the adult eye is incompletely understood. Here, we show that conditionally knocking out Vegfa in adult mouse retinal pigment epithelial (RPE) cells, which regulate retinal homeostasis, rapidly leads to vision loss and ablation of the choriocapillaris, the major blood supply for the outer retina and photoreceptor cells. This deletion also caused rapid dysfunction of cone photoreceptors, the cells responsible for fine visual acuity and color vision. Furthermore, Vegfa deletion showed significant down-regulation of multiple angiogenic genes in both physiological and pathological states, whereas the deletion of the upstream regulatory transcriptional factors HIFs did not affect the physiological expressions of angiogenic genes. These results suggest that endogenous VEGF provides critical trophic support necessary for retinal function. Targeting factors upstream of VEGF, such as HIFs, may be therapeutically advantageous compared with more potent and selective VEGF antagonists, which may have more off-target inhibitory trophic effects. PMID: 23093773

6. Unique biological action of Longevinex®

Unique anti-VEGF action of Longevinex® via microRNA20b

Furthermore, Longevinex® has been shown to exert unusual anti-VEGF action via controlling microRNA20b which controls angiogenesis. NIH researchers showed that Longevinex® down-regulated microRNA20b -1366-fold in rodent heart tissue, which was six-fold greater down-regulation than a single key ingredient (resveratrol -189 fold). So the biological action of Longevinex® is known.

7. **Off-label bevacizumab (Avastin) use for macular degeneration versus nutriceutical use of Longevinex®**

While the FDA may consider this petition unusual and subject to outright dismissal as it falls outside of existing FDA requirements, the petitioner calls attention to the fact that an unapproved drug is being widely used for the treatment of wet macular degeneration as off-label prescribing.\(^{14}\) The off-label use of Avastin appears to have been tolerated by FDA due to the initial unavailability of any other effective treatment for macular degeneration at the time. Lucentis was approved sometime after Avastin came into common use.

The FDA appears to have “looked the other way” due to the dire need of patients for this drug treatment.

In a similar fashion, Resveratrol Partners LLC pleads with the commissioner to consider this compassionate-use request.

\(^{14}\) MEDICARE PAYMENTS FOR DRUGS USED TO TREAT WET AGE-RELATED MACULAR DEGENERATION, Department of Health and Human Services OFFICE OF INSPECTOR GENERAL, Daniel R. Levinson Inspector General April 2012 OEI-03-10-00360
First oral agent to quell invasive macular degeneration, restore lost vision

Nutriceutical offers hope to those facing blindness

Ft. Lauderdale, FL (May 6, 2012) – There may be new found hope for patients whose vision is threatened when medicine injected directly into the eyes fails to cause abnormal blood vessels to recede. While injectable drugs called angiogenesis (an-gee-oh-jen-esis) inhibitors are considered a modern miracle and have become the standard of care for patients with the fast-progressive form of macular degeneration, they are not foolproof. For the first time researchers report that an oral nutriceutical, used on a last resort basis, rapidly restores vision to otherwise hopeless patients who face permanent loss.

Stuart Richer OD, PhD, Director, Ocular Preventative Medicine-Eye Clinic, James A. Lovell Federal Health Care Center, North Chicago, Illinois, says all other therapies were exhausted before employing the oral nutriceutical under compassionate-use protocols on a case-by-case basis. Usually most patients respond to medicine injected directly into the eyes, he says, but about one in three patients recover driving vision and one in six patients go on to experience permanent vision loss and others may refuse needle injections directly into the eyes, making them candidates for this rescue medicine.

Three successfully treated cases were presented at the annual Association For Research In Vision & Ophthalmology meeting in Ft. Lauderdale, Florida.

One striking case is an 88-year old woman whom retinal specialists said was beyond any help offered by conventional medicines or surgery. The nutriceutical helped this hospitalized woman...
regain her ability to see faces, read a menu and visualize her handwriting in just four days. “As she was an inpatient were also able to observe that her 40-year history of low-blood pressure and migraines improved after months of use,” said Dr. Richer.

In another case a 75-year old man with failing vision experienced recovery of vision in 5 days and was able to renew his driver’s license after taking just 7 nutriceutical capsules. Dr. Richer says 16 of the first 17 cases responded positively to nutriceutical medicine. There were no side effects reported. Because these patients faced impending loss of vision, for ethical reasons no patients received inactive placebo pills. He says it is unknown whether this nutriceutical produces such positive results in the more common dry form of macular degeneration, but the benefit to vision is typically observed in both eyes and is self-evident.

Dr. Richer says in these first cases he has monitored, blind spots (called scotomas) disappear, time to recover from bright light (glare recovery) is reduced, and contrast vision (shades of grey) as well as visual acuity (ability to see letters on a chart) generally improve within 3-6 weeks with the nutriceutical. “With our instruments we documented a more youthful appearance of retinal tissues as well as improved underlying circulation. There were also other improvements in health observed or measured outside of the eyes that were unanticipated,” notes Dr. Richer.

Only in recent years has there been a reliable way to treat wet macular degeneration, a disorder where abnormal blood vessels invade the visual center (macula) of the eyes. Any of three FDA-approved drugs, Avastin, Lucentis and Eylea, are needle-injected into the white of the eye to diminish the formation of these abnormal blood vessels. These are considered miracle drugs. Retreatment is usually necessary every six to eight weeks. However, since these drugs are not foolproof, oral antioxidant therapy was employed with measurable success.

Dr. Richer selected a particular nutriceutical mixture of vitamins and small herbal molecules (Longevinex®) because of its extensive testing and proven ability to favorably alter genes in a superior manner to other available nutriceuticals. Dr. Richer cautions that other similar store-bought products are not likely to produce the same rapid results seen among his patients. He advises patients not to risk their vision with unproven products. Nor should patients consider this oral medicine supplants injected medicine.

While the nutriceutical used in this report is non-prescription and directly available to patients and could be used alongside injected drugs, Dr. Richer advises physician consultation prior to its use. It still remains unproven until it is evaluated in broader studies, says Richer, who adds: “this oral nutriceutical taps into the newly appreciated science of epigenetics, where gene protein-making switches are favorably turned on and off, and suggests that age-related eye problems may not be inevitably progressive and biological age is not necessarily cast in stone.” There is newfound hope for recovery of lost vision, regardless of the patient’s image.
Dr. Richer has no financial interest in the products used in his investigations. To learn more or make a donation to further Dr. Richer’s research, visit Dr. Richer’s website at www.eyedoctorricher.com

Contact: Stuart Richer OD, Ph.D.
stuartricher1@comcast.net
847-409-4131

Ocular Coherence Tomography Digital Images

Caption: View left to right shows cases 1, 2 & 3 described above. Ocular Coherence Tomography digital images reveal rapid restoration of normal or more youthful retinal architecture accompanied by marked improvement in visual acuity.

Credit: Poster #286 ARVO Meeting 2012
Longevinex® was used to successful quell the first sign of arterial disease (flow-mediated dilatation) without significant side effects in a 6-month crossover study among 34 patients with metabolic disease. An abstract of that study is provided below: (Full paper in appendix)


**Modified resveratrol Longevinex® improves endothelial function in adults with metabolic syndrome receiving standard treatment.**

Fujitaka K, Otani H, Jo F, Jo H, Nomura E, Iwasaki M, Nishikawa M, Iwasaka T, Das DK

**Source**

Second Department of Internal Medicine, Kansai Medical University, Moriguchi 570-850, Japan.

**Abstract**

Resveratrol is known to improve endothelial function in animals, but little is known about its effect on human subjects. Metabolic syndrome (MetS) is a cluster of cardiovascular risk factors underlying endothelial dysfunction. We hypothesized that the modified resveratrol, Longevinex®, improves endothelial function in patients with MetS. Thirty-four patients who had been treated for MetS and lifestyle-related disease were randomly assigned to group A, in which Longevinex® was administered for 3 months and then discontinued for 3 months, whereas in the time-matched group B, Longevinex was administered between 3 and 6 months. These 2 groups of patients received similar drugs at baseline for diabetes mellitus, dyslipidemia, or hypertension. Flow-mediated dilatation significantly increased during the administration of Longevinex® but decreased to baseline 3 months after the discontinuation of Longevinex® in the group A patients. Conversely, in the group B patients, flow-mediated dilatation remained unchanged for the first 3 months without Longevinex® but was significantly increased 3 months after the treatment with Longevinex®. Longevinex® did not significantly affect blood pressure, insulin resistance, the lipid profile or inflammatory markers during 6-month follow-up. These results demonstrate that Longevinex® specifically improves endothelial function in subjects with MetS who were receiving standard therapy for lifestyle-related disease. PMID: 22118755
9. Ingredients, dosing and toxicity of Longevinex®

The ingredients in Longevinex® are as follows

![Longevinex® Supplement Facts](image)

**Animal toxicity**

Extensive animal toxicity data is provided in the appendix. Also Longevinex® was tested for kidney toxicity in humans.

**Cytotoxicity**

Cytotoxicity of Longevinex® was tested in two species (rats and rabbits) for a period of six months at doses up to 100 mg/kilogram of body weight of Longevinex® powder providing ~1000 mg of trans resveratrol, a dose which has previously been found to be cytotoxic (increases the area of scarring in an experimentally-induced heart attack). Longevinex® unexpectedly reduced the area of fibrosis in heart tissue at the highest
Hormetic response of resveratrol against cardioprotection.

Juhasz B, Mukherjee S, Das DK.

Abstract

Resveratrol, a grape- and red wine-derived polyphenolic phytoalexin, shows diverse health benefits including cardioprotection. Recent studies implicate that resveratrol displays hormetic action, protecting the cells at a lower dose while killing them at relatively higher doses. Because such hormetic behaviour may have a significant impact on epidemiological and clinical studies, the present study sought to determine dose-response curves for resveratrol action. In parallel, another resveratrol formulation was tested, namely, Longevinex (Resveratrol Partners LLC, USA). A group of rats were force-fed three different doses of resveratrol or Longevinex (2.5 mg/kg, 25 mg/kg and 100 mg/kg) for up to 30 days, while the control group was only given placebo. The results showed hormesis for pure resveratrol, which was cardioprotective at lower doses and detrimental for higher doses, but surprisingly Longevinex did not display any hormetic action. In the concentration range studied, Longevinex remained cardioprotective even at 100 mg/100 g body weight - a dose that killed 100% of the hearts when tested with pure resveratrol. To further test whether Longevinex doses are beneficial for other animal species, Longevinex was gavaged to a group of rabbits for six months, and showed exactly the same degree of cardioprotection. Cardioprotection was examined in isolated working hearts subjected to 30 min of ischemia followed by 2 h of reperfusion; left ventricular performance and infarct size was also examined. It appears that Longevinex does not show any hormetic action, while resveratrol clearly does.

PMID: 21264071
Longevinex® was found to reduce scarring (fibrosis) following an experimentally induced heart attack in laboratory rats at a human equivalent dose of 100 mg, far lower than prior studies involving plain resveratrol (175-350 mg). (See abstract below)


Effects of Longevinex® (modified resveratrol) on cardioprotection and its mechanisms of action.
Mukherjee S, Ray D, Lekli I, Bak I, Tosaki A, Das DK.

Source
Cardiovascular Research Center, University of Connecticut School of Medicine, Farmington, CT 06030-1912, USA.

Abstract

Although resveratrol has been proven to possess diverse health benefits, several recent reports have demonstrated conflicting results on some aspects of its effects, including its anti-aging properties. Considerable debate appears to exist on the dose and bioavailability of resveratrol, leading to the controversies on its effectiveness. To resolve the problem, we designed a study with a resveratrol formulation that contained resveratrol supplemented with 5% quercetin and 5% rice bran phytate (commercially known as Longevinex). These ingredients were micronized to increase the bioavailability. Sprague-Dawley rats were gavaged with either Longevinex or vehicle (5% quercetin plus 5% rice bran phytate), and rats were sacrificed after 1 or 3 months, when isolated working hearts were subjected to 30 min ischemia followed by 2 h of reperfusion. Longevinex-treated hearts, irrespective of the duration of treatments, revealed superior cardiac performance, reduced infarct size, and induction of survival signals as evidenced by increased Bcl2/Bax ratio and enhanced Akt phosphorylation. In contrast, LC3-II and Beclin were enhanced significantly after 3 months of Longevinex® treatment, suggesting that autophagy occurred only after feeding Longevinex to rats for a prolonged period of time. Corroborating with the results of autophagy, Sirt1 and Sirt3 increased significantly only after 3 months of Longevinex® treatment, suggesting that enhanced expression of Sirts correlated with induction of autophagy. In concert, Longevinex caused phosphorylation and nuclear translocation of FoxO1, FoxO3a, and FoxO4, indicating involvement of FoxOs with autophagy. Since Sirts and FoxOs are reliable markers of longevity, the results appear to suggest that Longevinex induces longevity after prolonged feeding via induction of autophagy, while it converts death signals into survival signals and provides cardioprotection within a relatively shorter period of time. PMID: 21076489
10. **Individually-perceived visual improvement versus pooled data**

In the small number of treated subjects, Longevinex® has exhibited meaningful patient-perceived improvement in best corrected visual acuity in an estimated 6 out of 10 treated patients (very small sample).

In a published study in order for patients subjectively perceive improvement in their vision when their visual acuity improves by 5 to 7 letters on the acuity chart. (See abstract below)

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**Graefes Archives Clinical Experimental Ophthalmology.** 2011 Sep 8.

### Subjective perception versus objective outcome after intravitreal ranibizumab for exudative AMD.

*Koch KR, Muether PS, Hermann MM, Hoerster R, Kirchhof B, Fauser S.*

**Source**

Center of Ophthalmology, University of Cologne, 50924, Cologne, Germany, konikoch@web.de.

**Abstract**

**BACKGROUND:**

The efficacy of ranibizumab in preserving visual acuity in exudative age-related macular degeneration (AMD) has been widely demonstrated. However, statistically significant improvements in outcome measures such as best-corrected visual acuity (BCVA) may not necessarily be clinically relevant. Clinical relevance can be assumed when the treatment success is perceivable for the patient. We therefore investigated the relation between subjective perception of the treatment success and the objective outcome after intravitreal ranibizumab treatment.

**METHODS:**

In this prospective interventional case series, patients received three monthly ranibizumab injections for exudative AMD. To assess the subjective study outcome (SSO) 4 weeks after the third injection, patients had to grade the overall trend of visual quality in the treated eye since baseline. Objective changes of functional (BCVA measured with ETDRS reading charts; reading visual acuity (RVA) and reading speed measured with Radner reading charts) and morphological parameters (central retinal thickness measured with OCT) were evaluated. Agreement between SSO and objective parameters was assessed with nonparametric statistical tests.
RESULTS:

Seventy-four eyes of 74 patients were analyzed. **Mean BCVA increased from 55 (SD ±13)**

**ETDRS letters by +3.16 letters** (SD ±11.99, p = 0.03). Mean RVA (measured as logRAD score) increased by -0.067 (SD ±0.294, p = 0.052). **Fifty patients (68%) perceived a subjective improvement, 16 (21%) no change, and eight (11%) a worsening in the study eye (SSO). SSO was independent of whether treating the better- or worse-seeing eye (p = 0.83).** SSO was significantly correlated with BCVA, RVA, and reading speed (as assessed using the critical print size (CPS)) changes (p = 0.002, p < 0.001, and p = 0.002), but showed no correlation to central retinal thickness changes (p = 0.783). Patients gaining ≥ +5 ETDRS letters had a significantly better SSO (p = 0.001). **The rate of subjective improvement increased distinctly to >80% among patients gaining ≥ +7 letters.**

CONCLUSIONS:

In this study, **2/3 of patients reported a subjective improvement from ranibizumab injections.** Patients’ perception was significantly correlated with objective changes in BCVA and reading visual acuity. Our data indicate that the **mean threshold for perceived improvement is a +5 to +7 letter gain,** which might accordingly be considered clinically meaningful and relevant. Patients’ perception was **independent of whether the better- or worse-seeing eye was treated.** PMID: 21901296

As presented above, researchers report that the threshold for patients reporting subjective improvement in vision is 5-to-7 letter gain using a standard visual acuity chart. In a small study (74 subjects/74 eyes) conducted in Europe, only 68% of patients perceived their vision had improved with the use of injectable ranibizumab (Lucentis®), while 21%
reported no change and 11% reported a worsening of their vision. Most of
the published studies group and average the visual benefits of anti-VEGF
treatment, but when one considers how many out of 100 patients truly
perceive their vision has improved, it is a much lower number than the
typical effectiveness percentage attributed to these drugs.

While an FDA press release (below) indicates ranibizumab (Lucentis®) was
approved because it was shown to maintain the vision of “more than 90% of
patients” with wet macular degeneration, the press release concedes that
only a third of these treated patients actually report visual improvement.
(See below) This means the majority of patients only benefit is that their
vision loss has not progressed while receiving monthly injections.

FDA NEWS RELEASE

FOR IMMEDIATE RELEASE
P06-94
June 30, 2006

FDA Approves New Biologic Treatment for Wet Age-Related Macular
Degeneration

The Food and Drug Administration (FDA) today approved Lucentis (ranibizumab injection) for
the treatment of patients with neovascular (wet) age-related macular degeneration (AMD).
Lucentis is the first treatment which, when dosed monthly, can maintain the vision of more
than 90 percent of patients with this type of AMD. Lucentis is a new molecular entity (NME),
meaning it contains an active substance that has never before been approved for marketing in any
form in the United States. Lucentis will be the first FDA--approved product to provide
prescription information in the new format for prescription drug package inserts, to provide
professionals and consumers clear and concise prescription information.

"This approval is of great importance for the 155,000 Americans who are diagnosed each year
with AMD, a common cause of severe and irreversible vision loss in older adults," said Dr.
Andrew von Eschenbach, Acting Commissioner of Food and Drugs. "At a time when our elderly
population is rapidly increasing, this product preserves quality of life for those affected by this
disease, helping them to regain the ability to participate in everyday activities such as reading
and driving."

AMD, a retinal disease causing severe and irreversible vision loss, is a major cause of blindness
in individuals older than 55 years. Untreated, the majority of eyes affected with wet AMD may
become functionally impaired. Wet AMD, which accounts for 10 percent of all AMD, is responsible for 80 percent of the associated vision loss.

The vision loss in wet AMD is caused by the growth of abnormal leaky blood vessels that eventually damage the area of the eye responsible for central vision. Lucentis is designed to block new blood vessel growth and leakiness, which ultimately lead to disease progression and such vision loss.

Lucentis, a biologic product, administered by injection into the eye, was shown to be safe and clinically effective in three multicenter, randomized studies of patients, representative of the population usually affected with AMD. In clinical trials, nearly 95 percent of the participants who received a monthly injection maintained their vision at 12 months compared to approximately 60 percent of patients who received the control treatment.

Approximately one-third of patients in these trials had improved vision at 12 months. In a single study carried out for 24 months, these findings have been maintained with continued monthly dosing. The most commonly reported adverse events included conjunctival hemorrhage, eye pain, floaters, increased eye pressure and inflammation of the eye. Serious adverse events were rare and often related to the injection procedure including endophthalmitis (severe inflammation of the interior of the eye), intraocular inflammation, retinal detachment, retinal tear, increased eye pressure and traumatic cataract.

Lucentis is manufactured by Genentech, Inc. in South San Francisco, California. 
#http://www.fda.gov/newsevents/newsroom/pressannouncements/2006/ucm108685.htm
Page Last Updated: 06/18/2009
11. Expansion of candidates

So it is very possible a larger number than the estimated 30,000 patients who progress to registered blindness actually continue to undergo expensive invasive instillation of medication without visual improvement and may benefit from use of an oral medication that specifically addresses the biological reason why treatment fails. Therefore, it may be found that concomitant use of both intraocular-injected VEGF-blockers plus oral nutriceutical therapy will be found to be compatible.
12. **Environmental impact**

There are no known environmental impact factors involved with the delivery of this oral nutriceutical to aged patients.
13. **Recent history of treatments for wet macular degeneration**

For background information, probably the best three review sources of information about recent treatments for wet macular degeneration for an uninformed reviewer would be:

Veritti D, Sarao V, Lenzetta P, Neovascular Age-Related Macular Degeneration, Ophthalmologica 2012;227 (Suppl. 1):11-20


All three reports are provided in full text in the accompanying appendix of this petition.
14. Economic impact of oral treatment for wet macular degeneration

Longevinex® as an oral nutriceutical offers the following potential economic and medical advantages:
   a. It does not involve a needle jab into the eye.
   b. It is far less costly than ranibizumab (Lucentis®)
   c. It is customarily consumed daily as an oral dietary supplement
   d. It may confer other health benefits apart from eye conditions
   e. It is not anticipated that Longevinex® would replace monoclonal antibody VEGF-blockers except possibly for patients who refuse needle injections.

<table>
<thead>
<tr>
<th>Cost factors of injected and oral anti-VEGF medications</th>
<th>Ranimizumab (Lucentis®)</th>
<th>Longevinex®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method of administration</td>
<td>Needle injection</td>
<td>Oral</td>
</tr>
<tr>
<td>Cost per single treatment dose</td>
<td>$2000</td>
<td>$0.90/day</td>
</tr>
<tr>
<td>Medicare payment</td>
<td>~$1564</td>
<td>$27.00/30-day supply</td>
</tr>
<tr>
<td>Physician injection fee</td>
<td>$180</td>
<td>$0</td>
</tr>
<tr>
<td>Frequency</td>
<td>Every 30-45 days</td>
<td>Daily oral dose Longevinex® may be found to prolong the interval between injections and reduce over-all costs (it may pay for itself) while improving visual outcomes.</td>
</tr>
</tbody>
</table>
15. Conclusions and Certification Statement

"The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petition which are unfavorable to the petition."

Identifying information-- The petition must be signed and include the petitioner's address and phone number.

Signature ____________________________________________
William Sardi, Executive partner
Name of petitioner: Resveratrol Partners LLC
Mailing address: 4760 Dewey Drive, Suite 117, Las Vegas, NV 89118-2289
Telephone number for purposes of this study: 909 596-9507
General office telephone: 702 462-7955
16. **THE HUMAN CLINICAL TRIAL**

**Patient enrollment**

Criteria for patient enrollment would be:

- Patients with wet macular degeneration whose vision has declined after 6 successive injections

Or

- Patients who refuse to have medication injected into their eyes

The eye physician would exercise decision making regarding continuation or abandonment of the injectable drug. The sponsor/applicant does not deem it has a role in ethical clinical decision making.

The patients would sign an informed consent that they understand the oral treatment is not FDA approved, that it is yet unproven, that it should not be employed in lieu of injectable drugs unless deemed by a physician to be in their best interest.
17. **Testing to be performed**

The study will measure:


(2) Snellen visual acuity

(3) Photostress recovery (as measured by Macular Adaptometer-Health Research Sciences, Lighthouse Point, Florida). See information below and appendix.

(4) *Spectral Domain* Optical Coherence Tomography

(5) Cataract grade.

Testing will be conducted at (a) baseline, (b) 6-weeks and (c) 6-months.

Data will be submitted to FDA at each time point and the study prolonged if data is positive.

Investigators will be approved based upon their ability to perform the above tests.
Visual Function Questionnaire


Scoring Manual

Development of the 25-item National Eye Institute Visual Function Questionnaire.
Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, Hays RD; National Eye Institute
Visual Function Questionnaire Field Test Investigators.

Source
Division of General Internal Medicine and Health Services Research, Department of Medicine,
UCLA, 911 Broxton Plaza, Box 951736, Los Angeles, CA 90095-1736, USA.

Abstract

OBJECTIVE:
To develop and test the psychometric properties of a 25-item version of the National Eye
Institute Visual Function Questionnaire (NEI VFQ-25).

DESIGN:
Prospective observational cohort study of persons with 1 of 5 chronic eye diseases or low vision
who were scheduled for non-urgent visits in ophthalmology practices and a reference sample of
persons without eye disease.

SETTING:
Eleven university-based ophthalmology practices and the NEI Clinical Center.

PATIENTS:
Eligible participants had to have 1 of the following eye conditions: age-related cataracts, age-
related macular degeneration, diabetic retinopathy, primary open-angle glaucoma,
cytomegalovirus retinitis, or low vision from any cause. Seven of the 12 sites also enrolled
persons in a reference sample. Reference sample participants had no evidence of underlying eye
disease but were scheduled for either screening eye examinations or correction of refractive error. All eligible persons had to be 21 years or older, English speaking, and cognitively able to give informed consent and participate in a health status interview.

MEASUREMENTS AND MAIN RESULTS:

To provide the data needed to create the NEI VFQ-25, all subjects completed an interview that included the 51-item NEI VFQ. Estimates of internal consistency indicate that the subscales of the NEI VFQ-25 are reliable. The validity of the NEI VFQ-25 is supported by high correlations between the short- and long-form versions of the measure, observed between-group differences in scores for persons with different eye diseases of varying severity, and the moderate-to-high correlations between the NEI VFQ-25 subscales that have the most to do with central vision and measured visual acuity.

CONCLUSIONS:

The reliability and validity of the NEI VFQ-25 are comparable to those of the 51-item NEI VFQ field test version of the survey. This shorter version will be more feasible in settings such as clinical trials where interview length is a critical consideration. In addition, preliminary analyses indicate that the psychometric properties of the NEI VFQ-25 are robust for the eye conditions studied; this suggests that the measure will provide reproducible and valid data when used across multiple conditions of varying severity.

PMID: 11448327
MDD-2 Macular Adaptometer

Description provided by the manufacturer

The MDD-2 Macular Adaptometer is a FDA Class 1 Medical Instrument that measures photostress recovery in the visual field of the eyes, enabling the early detection of retinal disease.

MDD stands for Macular Degeneration Detection and the MDD-2 is different from other optical equipment such as the OCT in that it measures the FUNCTION of the macular as opposed to viewing an image of the tissue to determine presence of pathology.

Use of the MDD-2 to assess central retinal eye health elevates the quality of care especially for those primary care doctors who may have no other way of determining central retinal (macular) function and thus health.

Benefits of MDD-2

- Rapid testing (less than 5-minutes for both eyes)
- Non-invasive
- Easy for any trained technician to perform the test
- Immediate result
- Does not require doctor's time

Features of the MDD-2

- Portable, hand-held instrument
- No supplemental software or computer required
- Four diffused xenon arc flash used to emit diffused light flash
- Built in IR & UV Block Filters
- Powered by USB Adapter
- No doctor required to interpret results

**How the MDD-2 test works**

1. The clinician places the viewing aperture of the instrument to the patient’s eye and performs the test monocularly.
2. The patient is instructed to look into the viewing aperture and asked to align the "zero" image displayed to the center of their vision by moving it accordingly.
3. The patient is informed that a bright flash is displayed after which a digital numeral is displayed. The patient should audibly speak the number once they are able to see it (this could take anywhere from 50 to 90 seconds)
4. When the patient speaks the number, the clinician depresses the button and a time measurement is taken.
5. Based on the measurement, the physician interprets the result and makes an appropriate recommendation.

Health Research Sciences, 5340 North Federal Highway, Suite 105, Lighthouse Point, Florida 33064

The MDD-2 photostress recovery device has been validated by comparison of normal eyes with eyes with wet macular degeneration.

<table>
<thead>
<tr>
<th>Photostress Recovery Times Using MDD-2 Instrument</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Eyes</td>
</tr>
<tr>
<td>Subjects 15-84 years of age</td>
</tr>
<tr>
<td>Initial flash, right eye</td>
</tr>
<tr>
<td>5-minute repeat, right eye</td>
</tr>
<tr>
<td>Initial flash, left eye</td>
</tr>
<tr>
<td>5-minute repeat, left eye</td>
</tr>
<tr>
<td>Wet Macular Degeneration</td>
</tr>
<tr>
<td>One eye tested per subject</td>
</tr>
<tr>
<td>(best corrected visual acuity 20/80-20/400; 25-2 letters)</td>
</tr>
<tr>
<td>No fluid, initial flash</td>
</tr>
<tr>
<td>No fluid, 5-minute repeat</td>
</tr>
<tr>
<td>With fluid, initial flash</td>
</tr>
</tbody>
</table>
Reproducible measurement of macular light flash recovery time using a novel device can indicate the presence and worsening of macular diseases.

Newsome DA, Negreiro M.

Source
Retinal Institute of Louisiana, New Orleans, Louisiana, USA. doctordave1618@aol.com

Abstract

PURPOSE:
To determine the safety, sensitivity, and specificity of a novel flash photorecovery timing instrument with response verification in differentiating normal from abnormal maculae, and in detecting worsening macular disease.

METHODS:
Right and left eye photorecovery times were determined at baseline and after 5 min using a xenon arc, flash filtered for infrared, ultraviolet, and visible short wavelengths, delivered through an aperture in a hand-held tube. A push-button actuated timer and flash and stopped timer when lighted numbers became visible post-flash. A numeric keypad verified responses. Normal subjects (two eyes tested, n = 144; one eye tested, n = 108) ranged in age from 15 to 84. Photorecovery times were measured in one eye of subjects with small drusen and 20/20 acuity (53-55 correct ETDRS letters; n = 57); in both eyes of subjects with dry age-related macular degeneration (AMD; n = 118); wet AMD with (n = 19) or without (n = 17) macular fluid; and eyes of diabetics with background retinopathy with (n = 19) or without (n = 17) macular retinal thickening. Once-weekly photorecovery measurements for 6 months in each eye of 10 dry AMD subjects and 10 dry diabetic maculopathy subjects provided longitudinal data.
RESULTS:

Normal subjects' mean right eye recovery time was 9.6 sec (+/- 1.9 SD); left 10.8 sec (+/- 1.0 SD). Photorecovery lengthened after age 55, nearly doubling that of young subjects by age 80. Macular edema, serous macular detachment, or worsened dry AMD were accompanied by prolonged photorecovery (p < .01). When abnormal new vessels or retinal thickening appeared in three serially followed patients, photorecovery at least doubled (p < .01). In all three, photorecovery prolongation occurred without clinical symptoms. None of the 499 tested subjects reported adverse events due to the flash testing.

CONCLUSIONS:

These findings support the usefulness of a reproducible light flash macular vision recovery measurement as an indicator of macular pathology and worsening disease.

PMID: 19219688
INFORMED STUDY CONSENT

Longevinex® Wet Macular Degeneration Trial

I testify that (a) I have undergone at least six unsuccessful injections of medicine that inhibits new blood vessel formation at the back of my eyes and that my eye physician has exhausted all proven therapies for my eye condition or (b) that I refuse to have medicine instilled directly into my eyes by needle injection, and therefore desire, or have been advised I need, an alternative by my eye physician.

Therefore, I (name) ____________________________ consent to participate freely in a 6 month ocular health study in which I will take 1 daily oral capsule of Longevinex® nutritional supplement containing herbal extracts and vitamins. It is believed, based on limited scientific studies, that this intervention is relatively safe and addresses your eye and visual problem(s).

For your participation, you initially receive two (2) boxes (2- month supply) of Longevinex® and agree to receive (three) free eye examinations with dilation at 6 weeks and 6 months after starting the capsules.

At the 6-week visit, you will receive 4 additional boxes for a total of a 6-month supply of Longevinex® capsules. The subsequent cost of the capsules is approximately $1/day – should you wish to continue taking this oral medication.

The capsules are preferably taken in the morning with a meal, and apart from medications. You agree to report any side effects such as headaches, skin rashes or sore heels or any rapid and serious decline in your vision. Should further care be required, you will be referred to a physician.
You have the right to end your participation in this study at any time without consequence regarding future care in our office. However, if you stop taking the pills, for any reason, please call our office

Name of office practice: ________________________________
Name of practitioner ________________________________

Date __________________
Witness __________________

COPY PROVIDED TO SUBJECT PARTICIPANT
Baseline Longevenix® AMD Study

DATA FORM (GREEN)

Date ____________ Subject Code ____________________
Investigator: __________________________________

<table>
<thead>
<tr>
<th>DATA: Longevinex Wet AMD Study</th>
<th>Baseline</th>
<th>6-week</th>
<th>6-month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual Function Questionnaire FQ25 (driving subscale)</td>
<td>15</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Best Log Mar Distance VA</td>
<td>R</td>
<td>L</td>
<td>R</td>
</tr>
<tr>
<td>SD OCT Macula</td>
<td>R</td>
<td>L</td>
<td>R</td>
</tr>
<tr>
<td>SDOCT Nerve Fiber Layer</td>
<td>R</td>
<td>L</td>
<td>R</td>
</tr>
<tr>
<td>Cataract grade</td>
<td>R</td>
<td>L</td>
<td>R</td>
</tr>
<tr>
<td>MDD-2 Photostress Recovery Time (seconds)</td>
<td>R</td>
<td>L</td>
<td>R</td>
</tr>
</tbody>
</table>

* Perform glare test last

Test data entered by (initials)

MDD-2 is Macular Degeneration Detection instrument made by Health Research Sciences

SDOCT is Spectral Domain Optical Coherence Tomography
Repeat testing at 6-weeks and 6-months
20.
Baseline Longevenix® AMD Study
Demographic Form

DATE ______________

Name (last, first, code# L1, L2, L3, L4………L50)
____________________________________________________________

Age (years)
____________________________________________________________

Smoking (pack years) ________

Family AMD History (mother/father/sibling)
________________________________________

Duration of Disease (yrs) ____________

AREDS Report #18 Grade

RPE Refraction (0,1) right (0,1) left
Soft drusen (0,1) right (0,1) left
Total Score (0,1,2) right (0,1,2) left
Total Score Both Eyes (0,1,2,3,4) – MUST BE 4

Medical History- diabetes / cardiovascular disease / cancer

________________________________________________________________

Medications-
Aspirin daily: YES NO
Supplements-
Supplements providing copper or iron: YES NO

Wine Drinking (5 ounce glasses, per week)

INCLUSION CRITERIA – SRNV referable net to retinal specialist or AREDs GRADE 4 retinopathy

EXCLUSION CRITERIA
Anemia
Coumadin (OK if not too thin and takes Longevinex® at different time of day)

INFORMED CONSENT
21.

Serious Adverse Reaction Report Form

LONGEVINEX®

Required reporting for any adverse events associated with the use of Longevinex® that cause hospitalization or a doctor’s office visit.

Date: ______________

Clinician:
________________________________________________________________________

Patient:
________________________________________________________________________

Age: ______________

Affected eye: R   L

Longevinex first recommended on date: ______________

Did this adverse reaction result in hospitalization or doctor's office visit? YES NO

Did the patient lose vision associated with use of the product? YES NO

Was the oral medication being taken concurrently with injectable anti-VEGF treatment? YES NO

Was the patient taking other medications which provoked a possible drug/drug reaction? YES NO

What was the quantity of product consumed at the time the adverse reaction was first experienced? __________

What is the prognosis of the patient?
________________________________________________________________________
Please return the box promptly to our offices so that we may investigate this matter fully. We shall reimburse you for the postage costs and any other costs.

Please forward this form via email to:

AdverseReactionReport@longevinex.com or call 866 405 4000 to have your AR recorded.
Open Letter To Ophthalmologists/Optometrists

by Bill Sardi

Recently a poster presentation at the Association for Research in Vision & Ophthalmology (ARVO post #286) 2012 meeting (Drs. Richer, Stiles and Ulanski -- James A Lovell Federal Health Care Center, Veterans Hospital - North Chicago), which documented the first cases of wet macular degeneration successfully treated with an oral agent, received some attention by the news media which may prompt questions from your patients. The following document is written to aid ophthalmologists in answering questions regarding this development.

The oral agent is a dietary supplement or so-called nutriceutical that is commercially available (Longevinex®, pronounced long-jev-in-ex) whose principal (but not only) active molecule is resveratrol (rez-vair-ah-troll). This positive report and others presented at ARVO may spawn "a resveratrol era" in ophthalmology as this natural molecule rapidly moves from the laboratory bench to clinical use.

Commercial disclosure and purpose

Let me explain that I write as the managing partner of a company that markets the specific nutriceutical used in the above mentioned study, so that you are aware of my commercial affiliation. Because of 8 years of prior experience in marketing this product, I have gained unique knowledge about resveratrol that needs to be passed along to interested ophthalmologists in order to avert certain problems and to comply with existing regulations. I do not primarily write to promote the product I am commercially involved with per se, I write to head off potential problems and misunderstandings that could forestall or even doom further advancements.

Not a drug

It is important to understand that resveratrol is not a drug. Nor is there any available resveratrol-based drug available for off-label use. Glaxo-Smith-Kline (GSK) abandoned further research for its SRT501 drug when a
5000 mg oral dose induced kidney failure among terminal multiple myeloma patients.

This leaves over 350 brands of unproved resveratrol dietary supplements to choose that vary widely in quality, dosage, shelf-life, purity, and proven action.

Since resveratrol is not a drug, manufacturers cannot claim their products prevent, treat or cure any disease. However, a resveratrol-based nutriceutical may in fact be found to do so and the FDA may declare it a drug if there is positive human clinical data, regardless of whether a New Drug Application (NDA) has been filed.

Nonetheless, researchers are free to report their findings without sanction by the FDA. However, there are regulatory issues involving human studies and compliance with institutional review board (IRB) requirements that are addressed below.

Ethical issues and standard of care

Regardless of how eager some ophthalmologists may be in recommending a resveratrol-based nutriceutical to their patients, there are certain constraints that demand judicious use.

Certainly, ophthalmologists are concerned about macular degeneration patients with neovascular disease who fail to respond to current anti-angiogenic monoclonal antibody treatment (Avastin, Lucentis), failures that are reported to represent 1 of 6 patients treated. Ophthalmologists may be tempted to reach for resveratrol pills for these patients, but there are complicating factors.

First, there is the standard of care, which is represented by Avastin/Lucentis. Physicians must meet this current standard of care, which means they can only utilize a resveratrol-based product if: (1) the patient fails all other existing therapy; (2) the patient refuses injections into the eye; (3) it is used alongside existing therapy but not as a replacement for it. Medico-legally, this would protect practicing physicians from stepping outside the current standard of care.
The first 17 human cases, which were treated on case-by-case basis (not a controlled study where a placebo pill was used) showed measurable vision improvement in 16 of 17 cases. (For ethical reasons, a placebo pill could not be used in these otherwise hopeless cases.) For now, resveratrol is confined to compassionate use protocols. Recognize that some patients however may elect to use such a pill on their own under self-directed care.

**IRBs, NDAs**

Second, if attempting to conduct a human clinical trial under the aegis of an institutional review board (IRB), many institutions refer their protocols to an FDA review board in Washington DC which demands an investigational new drug application (IND) before a resveratrol pill can be studied, which also means submission of animal and human toxicity and human safety data. To date, there is no resveratrol dietary supplement company that has submitted an IND. This may limit institutional use of any resveratrol supplement for research studies involving diseases. A research study intended to test for a structure and function claim (example: helps support healthy vision by activation of glutathione in the retina) is permissible by law but not embraced by the FDA.

**Potential toxicity**

Generally, resveratrol is an antioxidant (binds to copper) at low doses and promotes oxidation (releases copper) at high doses. This may explain why a mega-dose (5000 mg) induced kidney failure in humans. Clinicians should be made aware that more is not better, it is counterproductive. In an animal study, the human equivalent of 175 mg of resveratrol was successfully employed and reduced the size of an experimentally-induced heart attack whereas ten times that much resveratrol (1750 mg) increased the size of a heart attack.

The resveratrol pill used at the Veterans Hospital in North Chicago has undergone animal and human toxicity studies and is considered non-toxic (paper submitted for publication, results on file), and a 6-month study in two animal species (rabbits, mice) showed it was not cytotoxic (cell killing) at human equivalent at the human equivalent dose of 2800 mg, whereas the same dose of plain resveratrol will cause the rodent heart to “die” in an experimental model of heart attack. This is one reason why this product was chosen for human use by researchers.
In the above-mentioned rodent heart study, 100 mg of Longevinex® about doubled the positive effect of resveratrol in reducing the size of an experimentally induced heart attack, so lower doses can be superior to high doses if provided with co-factors.

**Potential side effects**

Generally speaking, resveratrol is a relatively safe molecule when given in higher-than-dietary doses. Eight years after resveratrol pills came into common use in North America, no deaths have been associated with resveratrol pill use. However, some temporary side effects have been reported.

Any potential side effects produced by resveratrol are self-limiting as resveratrol itself is rapidly metabolized (attached or conjugated to detoxification molecules sulfate and glucuronate) in the liver. Free unbound resveratrol is only initially available until it makes a few passes through the liver where it is conjugated with larger detoxification molecules (glucuronate, sulfate) and then it is too large to pass through cell walls and enter genetic machinery within cells.

Once conjugated (metabolized), resveratrol is non-bioavailable. But there is an advantage to liver metabolism of resveratrol. Free-unbound resveratrol only has a half-life of a few minutes whereas liver-metabolized resveratrol has a half-life of many hours. At the site of infection, inflammation of malignancy, an unzipping enzyme, glucuronidase, is up-regulated by up to 17-fold to produce free unbound resveratrol. This is nature’s drug delivery system. There are many mistaken references that claim resveratrol is not bioavailable.

Because it inhibits cytochrome p450 enzymes in the liver, resveratrol increases the availability of drug molecules that some patients take at the same time as resveratrol pills. This is similar to the well-known grapefruit juice effect with drugs. Clinicians should be forewarned to give instruction to their patients to take prescription medications at a different time of day than resveratrol pills.
For example, some patients taking blood pressure medications have reported their blood pressure transiently drops too low and they get a little dizzy if taking simultaneously with resveratrol pills. Once resveratrol is metabolized in the liver (attached to glucuronate, sulfate) it becomes temporarily non-bioavailable and its side effects are then self-limiting. Since resveratrol inhibits blood clotting, it should be taken at a different time of day than blood-thinning medications. However, many patients taking blood thinners have used it without reported problems. However, clinicians should be alert for skin bruising or bloody nose among their patients taking resveratrol and blood thinners.

Because resveratrol is solely a copper chelator (binder), it may induce a shortage of available copper which is needed for collagen production. Some users of mega-dose resveratrol pills report Achilles heel tendonitis with use, which is likely an indication of collagen breakdown. Patients with this symptom should back off of dosage or cease using till symptoms subside. Copper supplements are problematic as they are not stable in dietary supplements. Copper promotes neovascularization and should not be consumed in dietary supplements by patients with neovascular disease. Since resveratrol is a metal chelator and indirectly controls iron, and inhibits growth, it should not be used by growing children or fertile females who must replace minerals lost in menstruation. Young females report frontal headaches, fatigue and/or sleep disturbance when taking resveratrol. Older individuals who are anemic due to hidden blood loss or anemia of chronic inflammation, infection or malignancy, may report fatigue with use of resveratrol pills.

All of the ingredients in Longevinex® are TNF (tumor necrosis factor) inhibitors. Side effects of TNF inhibitors include: (1) skin rash; (2) stiff hands; (3) anxiety reactions; (4) flu-like symptoms (vomiting). In our experience, severely anemic individuals tend to report these symptoms, which has been rare.
Source of resveratrol

There are two primary types of resveratrol used in dietary supplements: (a) resveratrol extracted from a dietary source and (b) pure resveratrol produced by fermentation. The latter is more costly.

Of the botanical sources of resveratrol, while there are some 70 resveratrol-bearing plants, only are used to produce extracts: (1) Vitis vinifera (grape skin) and (2) Polygonum cuspidatum (Giant Knotweed). Resveratrol derived from grape skin is more expensive.

The majority of botanical extracts derive resveratrol from Giant Knotweed which also contains emodin, a molecule that provokes diarrhea in some patients. Giant Knotweed 10%, 20% and 50% extracts will contain a sufficient amount of emodin to trigger diarrhea in some patients. Extracts exceeding 80% should be used.

Biological action

While resveratrol is an antioxidant, it is not a strong antioxidant. Its primary advantage is that it is a copper-chelating small molecule that can enter genetic machinery and have a broad effect over the human genome. Compared to monoclonal antibodies which solely block the doorway to the Vascular Endothelial Cell (VEGF) receptor, resveratrol (a) down-regulates VEGF; (b) calms inflammation; (c) improves circulation via production of nitric oxide (vasodilating); (d) inhibits clotting; (e) influences a broad number of genes including down-regulation of hypoxia-inducing factor (HIF1) which is responsible for trigging VEGF.

Longevinex®, the dietary supplement selected for use by the investigators at the Veterans Medical Center in North Chicago, in an experimental animal model of heart attack, has been shown to down-regulate gene-controlling microRNA that target HIF and VEGF about six-fold better than plain resveratrol. For this reason, clinicians are warned that substitution with another brand of resveratrol may not exert the same effect that has been demonstrated with Longevinex®. The combination of nutrients in Longevinex® has been shown to work synergistically and in a superior manner to plain resveratrol.
Science versus price

Regardless of the science that backs any available brand of resveratrol pill, most senior adults make purchasing decisions based upon price. Their typical price point for out-of-pocket medical expenses like medicines is about $10.

Once macular degeneration patients learn that resveratrol is a key ingredient in these pills, our experience is that they will go shopping for the lowest cost pills, which often vary from the labeled dosage. For example, brands of resveratrol pills selling at big-box discounts stores often provide only micrograms or only a few milligrams of resveratrol. Yet the front of the bottle makes it appear resveratrol is its primary ingredient.

Also be aware that there are many devious online suppliers of resveratrol pills that are now attempting to direct traffic to their unproven products now that word is out that a resveratrol-based pill may remedy wet-macular degeneration. Some of these suppliers are planting false testimonies on the internet. This kind of outlaw marketplace could mislead macular degeneration patients and result in a missed opportunity to save vision. Not any resveratrol pill will do. You need to press this point to your patients.

Dose, hormesis and preconditioning

Hormesis is known as a beneficial biological response to a low-dose toxin. Resveratrol is perceived as a biological stressor as a molecular mimic of starvation (calorie restriction) and is known to exert a hormetic effect. Lack of oxygen (high altitude), food deprivation (fasting or calorie restriction) and exposure to mild doses of radiation (radon gas) are other hormetic agents.

A low dose of resveratrol (greater than what the diet provides) activates endogenous natural antioxidant enzymes (glutathione, catalase, superoxide dismutase, heme oxygenase) and adenosine and nitric oxide. This response to biological stress is considered the most profound in biology.

These protective antioxidants are generally activated immediately following an adverse event, such as a stroke, heart attack, etc. But the intermittent consumption of a modest dose of resveratrol will activate these protective
antioxidants prior to such an event. This is known as preconditioning. This is not a biological phenomenon that is produced by any known drug. The take-home lesson here is that mega-dose resveratrol negates hormesis and the pre-conditioning effect.
Take-home lessons about resveratrol:

- Temper the dose of resveratrol to avoid potential toxicity and to produce optimal benefits.
- Judiciously follow the standard of care and recommend resveratrol pills to proper candidates.
- Suggest patients take resveratrol at a different time of day than their medications.
- Carefully assess pro-angiogenic (pro-neovascular) agents in the patients’ diet and supplements. Copper is one such pro-angiogenic agent. Tobacco is also pro-angiogenic.
- Research studies may be thwarted by the FDA if pursuing disease prevention or treatment outcomes because of the requirement to file a New Drug Application (NDA). However, a human study designed to measure structure and function outcomes does not require a New Drug Application (NDA).
- For ethical reasons, the manufacturer of Longevinex® does not encourage placebo-based human clinical trials. Resveratrol pills should be compared against existing therapy.

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LONGEVINEX® is not intended to prevent, treat or cure any disease.