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(54) Title: TREATMENT OF EYE DISEASES USING OMEGA 3 FATTY ACIDS AND AA/EPA BLOOD RATIO

(57) Abstract: Compositions comprising high doses of omega 3 fatty acids for use in the treatment or amelioration of eye diseases. The omega 3 fatty acid dose is such that the arachidonic acid/ eicosapentaenoic acid mass ratio in the blood is in the range of 0.8 to 3, and preferably from 1 to 1.5.

Treatment of eye diseases using omega 3 fatty acids and AA/EPA blood ratio

Technical field of the invention

The present invention relates generally to the fields of medicine, foods, and health food supplements. More particularly, it relates to compositions comprising omega 3 fatty acids for use in the treatment of a disease, and in particular to compositions comprising eicosapentaenoic acid (EPA) and//or docosahexaenoic acid (DHA) for use in the treatment or amelioration of eye diseases.

Background of the invention

Macular edema occurs when fluid and protein deposits collect on or under the macula of the eye (a yellow central area of the retina) and causes it to thicken and swell (edema). The swelling may distort a person's central vision, as the macula is near the center of the retina at the back of the eyeball. This area holds tightly packed cones that provide sharp, clear central vision to enable a person to see detail, form, and color that is directly in the direction of gaze.

The etiologies of the macular edema are Diabetes, Wet macular degeneration and inflammation i.e secondary to intraocular surgery, uveitis.

Photoreceptors are the primary sensory neurons residing in the outer nuclear layer (ONL) of the vertebrate retina. Photoreceptor degeneration is a common cause of human visual impairments resulting from light damage, genetic changes, and aging. The low quality of life of persons with severe vision loss and the unfortunate nonrenewable nature of photoreceptors have inspired investigations ranging from photoreceptor rescue to photoreceptor replacement either with prosthetic devices or through biologic approaches such as retinal regeneration and cell transplantation. The retinal pigment epithelium (RPE) is developmentally and anatomically close to the neural retina. Unlike retinal neurons, RPE cells are nonneural and can reenter the cell cycle on stimulation. Furthermore, their progenies may differentiate into cell types other than RPE. The RPE shields the retina from excess incoming light. It supplies omega-3 fatty acids and glucose, the former for building photoreceptive membranes, the latter for energy. Retinal is supplied by the visual vitamin A cycle. Water is removed from the retinal side to the choroid side, at a rate of 1.4-11 microliters per square centimeter per hour. It maintains balance of pH, and routinely

phagocytoses the oldest outer segment discs of the photoreceptors. It has a self-contained immune system, which is connected with the immune system proper to either shut down interactions when healthy, and when there is disease, it teams up with the main immune controls. Finally, it secretes substances to help build and sustain the choroid and retina.

The retinal pigment epithelium also serves as the limiting transport factor that maintains the retinal environment by supplying small molecules such as amino acid, ascorbic acid and D-glucose while remaining a tight barrier to choroidal blood borne substances. Homeostasis of the ionic environment is maintained by a delicate transport exchange system.

Damage to photoreceptors and RPE cells can be caused by dry macular degeneration, macular dystrophies e.g. Retinitis pigmentosa, rod-cone dystrophy, Best dystrophy, adult vitelliform dystrophy, high myopia, diabetes and some other diseases, and by postoperations damages, e.g. retinal detachment.

Retinal Dystrophies and dry macular degeneration cause progressive damage to rod and cone photoreceptors and the retinal pigment epithelium cells and most patients eventually have reduced vision. Low grade chronic inflammation play a major role to the disease pathogenesis. Currently there is no treatment to stop progression or improve vision in these patients.

Macular degeneration, often age-related macular degeneration (AMD or ARMD), is a medical condition that usually affects older adults and results in a loss of vision in the center of the visual field (the macula) because of damage to the retina. It occurs in "dry" and "wet" forms. It is a major cause of blindness and visual impairment in older adults (>50 years). Macular degeneration can make it difficult or impossible to read or recognize faces, although enough peripheral vision remains to allow other activities of daily life.

Although some macular dystrophies affecting younger individuals are sometimes referred to as macular degeneration, the term generally refers to age-related macular degeneration (AMD or ARMD).

In the dry (nonexudative) form, cellular debris called drusen accumulates between the retina and the choroid, and the retina can become detached. In the wet (exudative) form, which is more severe, blood vessels grow up from the choroid behind the retina, and the

retina can also become detached. It can be treated with laser coagulation, and with medication that stops and sometimes reverses the growth of blood vessels.

In 2004, it was estimated that 8 million individuals had intermediate AMD, defined as bilateral drusen, and approximately 2 million had advanced AMD, either neovascular AMD or geographic atrophy. Although intraocular drugs that inhibit vascular endothelial growth factor are currently available for treatment of neovascular AMD, no effective therapies are proven for atrophic AMD. Without more effective ways of slowing progression, the number of persons with advanced AMD is expected to double over the next 20 years, resulting in increasing socioeconomic burden.

DHA is a major structural component of the retina, and EPA may play a role as a precursor to signaling molecules with potential to influence retinal function, providing biological bases for testing these nutrients. Previous dose-ranging studies provided support for the doses used (Huang et al., 2008. Invest Ophthalmol Vis Sci. 49(9):3864-3869).

Retinal Dystrophy is not one single condition but the general name given to a wide range of eye conditions (for example, Retinitis Pigmentosa). 'Dystrophy' means a condition that a person is born with, 'retinal' means relating to the retina - the light sensitive film at the back of the eye. Most retinal dystrophies are genetic.

Classification of retinal dystrophies can be confusing because they are both clinically and genetically heterogeneous. There are several disease classification schemas and could be presented as (1) progressive vs stationary, and (2) central (macular) dystrophies vs generalized.

So, retinal Dystrophy occurs in a wide range of eye conditions and can be divided into two main groups:

1.- Isolated retinal dystrophies:

• Early onset retinal dystrophies, for example, Leber Congenital Amaurosis

• Rod-Cone Dystrophies, where the rods are the first part of the retina to be affected, for example, Retinitis Pigmentosa

• Cone-Rod Dystrophies where the cones are the first part of the retina to be affected

• Macular dystrophies, such as Stargardts disease, Best's disease

2.- Syndromic retinal dystrophies, for example:

• Usher Syndrome

• Batten Disease

• Bardet-Biedl

For wet AAMD, antiangiogenics or anti-VEGF agents can cause regression of the abnormal blood vessels and improve vision when injected directly into the vitreous humor of the eye. The injections must be repeated monthly or bimonthly. Several antiangiogenic drugs have been approved for use in the eye by the U.S. Food and Drug Administration and regulatory agencies in other countries.

Photodynamic therapy has also been used to treat wet AMD. The drug verteporfin is administered intravenously; light of the correct wavelength is then applied to the abnormal blood vessels. This activates the verteporfin and obliterates the vessels.

Some evidence supports a reduction in the risk of AMD with increasing intake of two carotenoids, lutein and zeaxanthin

Consuming omega-3 fatty acids (docosahexaenoic acid and eicosapentaenoic acid) has been correlated with a reduced progression of early AMD, and in conjunction with low glycemic index foods, with reduced progression of advanced AMD (Chiu et al., 2009. Br J Ophthalmol 93 (9): 1241–6). Central geographic atrophy, the "dry" form of advanced AMD, results from atrophy of the retinal pigment epithelial layer below the retina, which causes vision loss through loss of photoreceptors (rods and cones) in the central part of the eye. No medical or surgical treatment is available for this condition; however, vitamin supplements with high doses of antioxidants, lutein and zeaxanthin, have been suggested by the National Eye Institute and others to slow the progression of dry macular degeneration and, in some patients, improve visual acuity. Higher beta-carotene intake was associated with an increased risk of lung cancer.

Cell based therapies using bone marrow stem cells as well as Retinal pigment epithelial transplantation have been reported as experimental options in several patients

They are 3 types of retinal dystrophies that dietary treatment can help (gyrate atrophy, Refsum syndrome, and abetalipoproteinemia). Elevated serum phytanic acid levels are diagnostic. Avoiding foods high in phytanic acid (eg, fat and butter) and plasmaphoresis help to improve all neurologic signs.

Bassen-Kornzweig syndrome (abetalipoproteinemia) is due to malabsorption of cholesterol, fats, and fat-soluble vitamins from the small intestine. Deficiencies of vitamin A and vitamin E cause failure to thrive, peripheral neuropathy with muscle weakness, spinocerebellar ataxia, and RP. Vitamin A (300 IU/kg/day) and vitamin E (100 IU/kg/day) restore function and slow the progression of retinal degeneration.

There is also interest in whether vitamin A supplementation can help other forms of RP. A randomized controlled study sponsored by the National Institutes of Health (NIH) looking at vitamin therapy for RP in adults showed that vitamin A(15 000 IU) delays the progression of cone ERG loss. The same study showed that vitamin E (400 IU) may have a deleterious effect on RP patients.

However, these results have not been universally accepted in ophthalmic centers (Norton 1993. Arch Ophthalmol. 111:1460; author reply 1463–1465).

Dry eye syndrome, or dry eye disease, occurs when the eyes do not make enough tears, or the tears evaporate too quickly because the oil glands are blocked or abnormal.

This leads to the eyes drying out and becoming inflamed (red and swollen) and irritated.

The condition is also known as dry eyes or keratoconjunctivitis sicca. If the main problem is a blockage of the oil-secreting glands, then the condition is called blepharitis, meibomian gland dysfunction or lid margin disease.

Keratoconjunctivitis sicca (KCS), also called keratitis sicca, xerophthalmia or dry eye syndrome (DES) is an eye disease caused by eye dryness, which, in turn, is caused by either decreased tear production or increased tear film evaporation. It is found in humans and some animals. KCS is the most common eye disease, affecting 5 - 6% of the population. Prevalence rises to 6 - 9.8% in postmenopausal women, and as high as 34% in the elderly. The phrase "keratoconjunctivitis sicca" is Latin, and its translation is "dry [inflammation] of the cornea and conjunctiva"

There are no medical effective treatment available for the above conditions, and there is a need for more effective and/or alternative therapies for treating dry macular degeneration and retinopathies.

Brief description of the invention

The present invention provides novel compositions and dosage forms comprising omega 3 fatty acid for use in the treatment or amelioration of retinal diseases, such as macular degeneration and retinal dystrophies. The inventor treated a group of patients with eye diseases, particularly macular oedema due to wet macular degeneration, diabetes or inflammation, damage to photoreceptors and/or RPE cells and/or severe dry eyes, and shows that:

1) results are better using higher doses of EPA/DHA compared to previous art known doses.

2) results are better if dose of EPA/DHA its adjusted so that the blood ratio of AA/EPA is 1-1.5

Thus, **a first aspect** of the present invention refers to a composition, hereinafter composition of the invention, comprising at least 6 g of omega 3 fatty acids. In a preferred embodiment of the first aspect of the invention, the composition of the invention comprises at least 7 g of omega 3 fatty acids, more preferably 7.5 g of omega 3 fatty acids, more preferably at least 8 g of omega 3 fatty acids, more preferably at least 10 g of omega 3 fatty acids, and more preferably, at least 15 g of omega 3 fatty acids.

In another preferred embodiment of the first aspect of the invention, the composition of the invention comprises from 6 g to 15 g of omega 3 fatty acids, more preferably from 7.5 g to 15 g of omega 3 fatty acids, a more preferably from 8 g to 15 g of omega 3 fatty acids, and still more preferably from 8 g to 10 g of omega 3 fatty acids.

In another preferred embodiment of the first aspect of the invention, the omega 3 fatty acid is selected from the list consisting of: eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), alpha liniolenic acid (ALA), stearidonic acid (SA), oeicosatetraenoic acid, or

any combination thereof. In a more preferred embodiment of the first aspect of the invention, the omega 3 fatty acid is eicosapentaenoic acid (EPA).

In a further preferred embodiment of the first aspect of the invention, the omega 3 fatty acids are a combination of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). In a still further preferred embodiment of the first aspect of the invention, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are in a mass ratio from 1:1 to 5:1. Still more preferably, the eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are in a mass ratio of about 2:1.

In a still further preferred embodiment of the first aspect of the invention, said composition is a pharmaceutical composition which optionally comprises an acceptable pharmaceutical carrier and/or additional active ingredients. Preferably, the additional active ingredients are selected from the list consisting on antioxidants, lutein, zeathanthine, sesamol,GLA (Gamma linolenic acid) and *Aloe vera*, or any combination thereof.

More preferably, the pharmaceutical composition comprises at least 30%, and preferably at least 50% weight omega 3 fatty acids.

In another preferred embodiment, the composition is an oral dosage form. More preferably the oral dosage form is selected from the group comprising tablets, capsules, caplets, slurries, sachets, solutions, suspensions, chewing gum, and powder formulation that may be dissolved in a liquid. In a still more preferably embodiment, the oral dosage form is a suspension. In another still more preferably embodiment, the oral dosage form is a powder.

In another preferred embodiment, the composition of the invention is a food composition or a health food supplement. Preferably, the food composition optionally comprises an additional active ingredients additional active ingredients, preferably are selected from the list consisting on antioxidants, lutein, zeathanthine, sesamol, ,GLA (Gamma linolenic acid) and Aloe vera. More preferably, the food composition comprises at least 30%, and preferably at least 50% weight omega 3 fatty acids.

A **second aspect** of the invention refers to a kit of parts comprising eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in a mass ratio from 1:1 to 5:1.

In a preferred embodiment of the second aspect of the invention, the eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are a mass ratio of about 2:1.

In a still further preferred embodiment of the second aspect of the invention, said kit of parts is a pharmaceutical kit of parts which optionally comprises an acceptable pharmaceutical carrier and/or additional active ingredients. More preferably, the additional active ingredient is an antioxidant or a nutritional supplement. Still more preferably are selected from the list consisting on antioxidants, lutein, zeathanthine, sesamol, ,GLA (Gamma linolenic acid) and Aloe vera.

In another embodiment of the first aspect of the invention, said kit of parts is a food composition.

A **third aspect** of the inventions refers to the composition or the kit of parts of the invention, for use in therapy or for use as a medicament.

A **fourth aspect** of the invention refers to the composition or the kit of parts of the invention, for its use in the treatment or amelioration of eye diseases.

In a preferred embodiment of the fourth aspect of the invention the eye disease is macular oedema due to wet macular degeneration, diabetes or inflammation. More preferably, for the treatment of macular oedema, the composition or the kit of parts of the invention comprises an antiangiogenic or a steroid as active ingredient.

In another preferred embodiment of the fourth aspect of the invention, the eye disease is the damage to photoreceptors and/or RPE cells. More preferably, the damage to photoreceptors and/or RPE cells is selected from the list consisting of dry macular degeneration, macular dystrophies, high myopia, diabetes, postoperative damage or any combination thereof.

In a preferred embodiment of the fourth aspect of the invention, the macular degeneration is dry macular degeneration. In another preferred embodiment of the fourth aspect of the invention, the retinal dystrophies are selected from the list consisting on: Retinitis pigmentosa, rod-cone dystrophy, Best dystrophy, adult vitelliform dystrophy, or any combination thereof.

In another preferred embodiment of the fourth aspect of the invention, the eye disease is severe dry eyes (keratoconjunctivitis sicca or xerophthalmia).

In a more preferred embodiment, the pharmaceutical composition or kit of parts of the invention, or a composition or kits of part comprising eicosapentaenoic acid and docosahexaenoic acid, can be administered one or more times a day, for example, 1, 2, 3 or 4 times a day, in a typical total daily amount to be above 7 g per day of omega 3 fatty acids, more preferably to be above 8 g per day of omega 3 fatty acids, more preferably to be above 7 g per day of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and more preferably to be above 8 g per day. Preferably, the combined dosage is from 7.5g to 15 g per day. In a more preferred embodiment, the pharmaceutical composition or kit of parts of the invention can be administered in a dose wherein the combined EPA and DHA is such that the arachidonic acid/ eicosapentaenoic acid mass ratio in the blood is in the range of 0.8 to 3, and more preferably from 1 to 1.5.

In a more preferred embodiment, the food composition of the invention, or a food composition comprising eicosapentaenoic acid and docosahexaenoic acid, can be administered one or more times a day, for example, 1, 2, 3 or 4 times a day, in a typical total daily amount to be above 7 g per day of omega 3 fatty acids, more preferably to be above 8 g per day of omega 3 fatty acids, more preferably to be above 7 g per day of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and more preferably to be above 8 g per day. Preferably, the combined dosage is from 7.5g to 15 g per day. In a more preferred embodiment, the pharmaceutical composition or kit of parts of the invention can be administered in a dose wherein the combined EPA and DHA is such that the arachidonic acid/ eicosapentaenoic acid mass ratio in the blood is in the range of 0.8 to 3 preferably between 1 to 1.5.

Description of the figures

Fig. 1. Shows the number of eyes and the eye pathology.

Fig. 2. Visual acuity gain in letters. The eyes that had the greatest gain in vision were those who were taking 8-10g/day. Patients taking 8-10g day had 12.85 letters gain at 6 months and patients taking 5g/day had 10.57 letters gain at 6 months. Average gain is 11.85 letters at 6 months.

Fig 3. Shows the number of letters gained according to the AA/EPA ratio of each eye. Patients with a ratio between 1 and 1.50 had 15.67 letters gained. Patients with a ratio of 1.51 to 1.99 had 11.11 letters gained and patients with >2 ratio had 7.94 letters gained.

Detailed description of the invention

The present invention confronts the problem of to improve visual acuity and visual fields in patients with dry macular degeneration and retinal dystrophies.

It has been found by the inventor that significant improvements in the visual acuity (using the EDTRS electronic chart) and in signs and symptoms of these conditions can be achieved using high doses of EPA, and preferably of EPA and DHA, in the indicated ratio and dosage amounts. The therapy is effective even for patients who are non-responsive or poorly responsive to other therapies. The therapy of the invention is particularly suitable for oral administration.

In some embodiments, the EPA and DHA are for use together with a further therapeutic agent for simultaneous, sequential or separate administration. Preferably the further therapeutic agent is a steroid, an antiangiogenic drug like e.g. anti-VEGF, and/or immunosuppressive drug and/or other nutritional supplement.

The compositions and kit of parts of the invention can be used in dry macular degeneration and retinal dystrophies. High doses omega 3 fatty acid supplementation may represent a significant therapeutic option for such patients.

COMPOSITIONS AND KIT OF PARTS OF THE INVENTION

Thus, in accordance with a first aspect of the present invention, there is provided a composition, hereinafter composition of the invention, comprising at least 6 g of omega 3 fatty acids, In a preferred embodiment of the first aspect of the invention, the composition of the invention comprises at least 7.5 g of omega 3 fatty acids, more preferably at least 8 g of omega 3 fatty acids, more preferably at least 10 g of omega 3 fatty acids, and more preferably, at least 15 g of omega 3 fatty acids.

In a preferred embodiment of the first aspect of the invention, the composition of the invention comprises from 6 g to 15 g of omega 3 fatty acids, more preferably from 7.5 g to 15 g of omega 3 fatty acids, and still more preferably from 8 g to 15 g of omega 3 fatty acids.

An omega-3 fatty acid is an unsaturated fatty acid containing a final carbon-carbon double bond as the third bond from the alkyl end of the molecule (i.e. the end that is remote from the carboxylic acid group). Examples of omega-3 fatty acids are indicated in Table 1.

Table 1: Omega-3 fatty acids

Common name	Lipid name	Chemical name	MW
Tetracosahexaenoic acid	24:6 (*n*-3)	*all-cis*-6,9,12,15,18,21-tetracosahexaenoic acid	357
Tetracosapentaenoic acid	24:5 (*n*-3)	*all-cis*-9,12,15,18,21-tetracosapentaenoic acid	359
Docosahexaenoic acid (DHA)	22:6 (*n*-3)	*all-cis*-4,7,10,13,16,19-docosahexaenoic acid	328
Docosapentaenoic acid (DPA)	22:5 (*n*-3)	*all-cis*-7,10,13,16,19-docosapentaenoic acid	331
Eicosapentaenoic acid (EPA)	20:5 (*n*-3)	*all-cis*-5,8,11,14,17-eicosapentaenoic acid	302

Eicosatetraenoic acid (ETA) 20:4 (n-3) *all-cis*-8,11,14,17-eicosatetraenoic acid 304

Eicosatrienoic acid (ETE) 20:3 (n-3) *all-cis*-11,14,17-eicosatrienoic acid 306

Stearidonic acid (SDA) 18:4 (n-3) *all-cis*-6,9,12,15-octadecatetraenoic acid 276

Linolenic acid (ALA) 18:3 (n-3) *all-cis*-9,12,15 -octadecatrienoic acid 278

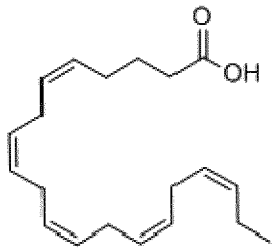
Hexadecatrienoic acid (HTA) 16:3 (n-3) *all-cis*-7,10,13 -hexadecatrienoic acid 250

In a preferred embodiment of the first aspect of the invention, the omega 3 fatty acid is selected from the list consisting of: eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), alpha liniolenic acid (ALA), stearidonic acid (SA), eicosatetraenoic acid (ETA), or any combination thereof. In a preferred embodiment of the first aspect of the invention, the omega 3 fatty acid is eicosapentaenoic acid (EPA). As is shown in examples, a minimum of 7500 mg (7.5 g), preferably 8.000 mg (8.0 g) of EPA is required to observe clinically useful outcomes.

In a further preferred embodiment of the first aspect of the invention, the omega 3 fatty acids are a combination of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), or any of their salts, ester, solvates, prodrugs, derivatives or analogs of EPA and DHA, or any combination thereof. In a still further preferred embodiment of the first aspect of the invention, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are use in a mass ratio from 1:1 to 5:1. Preferably is in the range of from 1:1 to 4:1, more preferably 1:1 to 3:1, still more preferably 1.5:1 to 2.5:1, yet more preferably 2.1:1 to 2.4:1,

most preferably in the range of from 2.1:1 to 2.2:1. Still more preferably, the eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are in a mass ratio of about 2:1.

As defined in the present invention, eicosapentaenoic acid (EPA or also icosapentaenoic acid), CAS Registry Number: 10417-94-4, IUPAC name (5*Z*,8*Z*,11*Z*,14*Z*,17*Z*)-5,8,11,14,17-icosapentaenoic acid is an omega-3 fatty acid. In physiological literature, it is given the name 20:5(n-3). It also has the trivial name timnodonic acid. In chemical structure, EPA is a carboxylic acid with a 20-carbon chain and five *cis* double bonds; the first double bond is located at the third carbon from the omega end. Is a compound of formula (I):

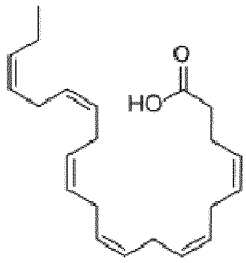


Formula (**I**)

or any of their salts, ester, solvates, prodrugs, derivatives or analogs thereof.

EPA is a polyunsaturated fatty acid (PUFA) that acts as a precursor for prostaglandin-3 (which inhibits platelet aggregation), thromboxane-3, and leukotriene-5 groups (all eicosanoids).

As defined in the present invention, docosahexaenoic acid (DHA) is an omega-3 fatty acid that is a primary structural component of the human brain, cerebral cortex, skin, sperm, testicles and retina. It can be synthesized from alpha-linolenic acid or obtained directly from maternal milk or fish oil.DHA's structure is a carboxylic acid(~oic acid) with a 22-carbon chain (docosa- is Greek for 22) and six (Greek "hexa") cis double bonds (-en~);[2] the first double bond is located at the third carbon from the omega end. Its trivial name is cervonic acid, its systematic name is *all-cis*-docosa-4,7,10,13,16,19-hexa-enoic acid, and its shorthand name is 22:6(n-3) in the nomenclature of fatty acids. CAS Registry Number: 6217-54-5, IUPAC name (4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-docosa-4,7,10,13,16,19-hexaenoic acid; Doconexent. Is a compound of formula (II):



Formula (**II**)

or any of their salts, ester, solvates, prodrugs, derivatives or analogs thereof.

As used herein, the term "derivative" includes both pharmaceutically acceptable compounds, i.e., derivatives of the compound of formula (**I**) or (**II**) which can be used in the preparation of a medicament, such as derivatives pharmaceutically unacceptable, as these may be useful in the preparation of derivatives pharmaceutically acceptable or the preparation of food compositions.

Also within the scope of this invention are prodrugs of the compounds of formula (**I**) or (**II**). The term "prodrug" as used herein includes any compound derived from a compound of formula (**I**) or (**II**), for example, esters, including carboxylic acid esters, amino acid esters, phosphate esters, sulphonate esters of metal salts, etc. carbamates, amides, etc.. that, when administered to an individual is capable of providing, directly or indirectly, said compound of formula (**I**) or (**II**) in said individual. Advantageously, said derivative is a compound that increases the bioavailability of the compound of formula (**I**) or (**II**) when administered to an individual or enhancing the release of the compound of formula (I) in a biological compartment. The nature of said derivative is not critical provided it can be administered to an individual and provides the compound of formula (**I**) or (**II**) in a biological compartment of an individual. The preparation of said prodrug may be performed by conventional methods known to those skilled in the art.

In some embodiments, the EPA and/or DHA are in the form of a salt. Suitable salts include those formed with organic or inorganic bases. Pharmaceutically acceptable base salts include, but are not limited to, ammonium salts, alkali metal salts, for example those of potassium and sodium, alkaline earth metal salts, for example those of calcium and magnesium, and salts with organic bases, for example dicyclohexylamine, N-methyl-D-glucomine, morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine, for example ethyl-, tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or

dimethyl- propylamine, or a mono-, di- or trihydroxy lower alkylamine, for example mono-, di- or triethanolamine.

In other embodiments, the EPA and/or DHA is/are in the form of an ester. Ester groups include those formed from the terminal carboxylic acid moiety of the omega-3 fatty acid and an alcohol, such as a C_{1-12} alkyl ester, formed by reaction of the omega-3 fatty acid with an alcohol having from 1 to 12 carbons, preferably a C_{1-6} alkyl ester formed by reaction of the omega-3 fatty acid with an alcohol having from 1 to 6 carbons, for example a methyl, ethyl, *n*-propyl, *iso*propyl, butyl, pentyl, or hexyl ester, formed by reaction of the omega-3 fatty acid with methanol, ethanol, *n*-propanol, *iso*-propanol, butanol, pentanol or hexanol. Preferably, the ester is an ethyl ester or a methyl ester, more preferably an ethyl ester.

In one preferred embodiment the EPA or salt or ester thereof comprises EPA and/or EPA ethyl ester, and the DHA or salt or ester thereof comprises DHA and/or DHA ethyl ester. More preferably, a combination of eicosapentaenoic acid and docosahexaenoic acid is used (i.e. the free acids of EPA and DHA are used, rather than salts or esters).

In a still further preferred embodiment of the first aspect of the invention, said composition is a pharmaceutical composition which optionally comprises an acceptable pharmaceutical carrier and/or additional active ingredients. More preferably, the pharmaceutical composition comprises at least 50% weight omega 3 fatty acids. Preferably, the composition comprises at least 30 weight % omega-3 fatty acids, more preferably at least 40 weight % of omega-3 fatty acids, still more preferably at least 50 weight % omega-3 fatty acids. Preferably, the composition comprises at least 30 weight %, more preferably at least 40 weight %, still more preferably at least 50 weight % of eicosapentaenoic acid. More preferably, the composition comprises at least 40 weight % of a combination of eicosapentaenoic acid and docosahexaenoic acid in a weight ratio of from 1:1 to 4: 1 , optionally in liquid form, more preferably at least 50 weight % of a combination of eicosapentaenoic acid and docosahexaenoic acid in a weight ratio of from 1:1 to 4:1, optionally in liquid form. In one particularly preferred embodiment, the composition comprises about 60 weight % of a combination of eicosapentaenoic acid and docosahexaenoic acid in a weight ratio of about 2:1, optionally in liquid form.

In another preferred embodiment, the composition is an oral dosage form. More preferably the oral dosage form is selected from the group comprising tablets, capsules, caplets, slurries, sachets, solutions, suspensions, chewing gum, and powder formulation that may

be dissolved in a liquid. In a still more preferably embodiment, the oral dosage form is a suspension. In another still more preferably embodiment, the oral dosage form is a powder.

In another preferred embodiment, the composition of the invention is a food composition or a health food supplement. Preferably, the composition comprises at least 30 weight % omega-3 fatty acids, more preferably at least 40 weight % of omega-3 fatty acids, still more preferably at least 50 weight % of omega-3 fatty acids. Preferably, the composition comprises at least 30 weight %, more preferably at least 40 weight %, still more preferably at least 50 weight % of eicosapentaenoic acid. More preferably the composition comprises at least 40 weight % of a combination of eicosapentaenoic acid and docosahexaenoic acid in a weight ratio of from 1:1 to 4:1, optionally in liquid form, more preferably at least 50 weight % of a combination of eicosapentaenoic acid and docosahexaenoic acid in a weight ratio of from 1:1 to 4: 1 , optionally in liquid form. In one particularly preferred embodiment, the composition comprises about 60 weight % of a combination of eicosapentaenoic acid and docosahexaenoic acid in a weight ratio of about 2:1, optionally in liquid form.

Preferred food compositions are selected, but not limited, from: a beverage, infused food, milk, yogurt, cheese, fermented milk, flavoured milk drink, soybean milk, precooked cereals, bread, cake, butter, margarine, sauces, frying oils, vegetable oils, corn oil, olive oil, soybean oil, palm oil, sunflower oil, cottonseed oil, condiments, salad dressings, fruit juices, syrups, desserts, icings and fillings, soft frozen products, confections, chewing gum and intermediate food.

The omega fatty acids EPA and DHA or salts or esters thereof, may be administered simultaneously, sequentially or separately. Then a second aspect of the invention refers to a kit of parts, hereinafter kit of parts of the invention, comprising eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in a mass ratio from 1:1 to 5:1. Preferably is in the range of from 1:1 to 4:1, more preferably 1:1 to 3:1, still more preferably 1.5:1 to 2.5:1, yet more preferably 2.1:1 to 2.4:1, most preferably in the range of from 2.1:1 to 2.2:1. Still more preferably, the eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are in a mass ratio of about 2:1.

In a still further preferred embodiment of the second aspect of the invention, said kit of parts is a pharmaceutical kit of parts which optionally comprises an acceptable pharmaceutical carrier and/or additional active ingredients. More preferably, the additional

active ingredient is an antioxidant or a nutritional supplement. Other agents may be additional nutritional products such as polyphenols and other antioxidants. In one preferred embodiment, the further active ingredient is an antioxidant or a nutritional supplement. Still more preferably are selected from the list consisting on antioxidants, lutein, zeathanthine, sesamol, GLA (Gamma linolenic acid) and *Aloe vera*, or any combination thereof.

In other preferred embodiment, the composition is substantially free from antioxidants selected from the list consisting of vitamin E (including tocopherols and tocotrienols), epigallocatechin-3-gallate (EGCG), vitamin C, lutein and zeaxanthin. In another preferred embodiment, the composition is substantially free from anti-oxidants. In another preferred embodiment, the composition contains no anti-oxidants.

In another embodiment of the first aspect of the invention, said kit of parts is a food kit of parts.

The kit of parts may comprise separate formulations of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The separate formulations of EPA and DHA may be administered sequentially, separately and/or simultaneously (optionally repeatedly). Thus, the two active ingredients can be administered either as a part of the same composition (food or pharmaceutical composition) or in separate compositions (food or pharmaceutical compositions). EPA can be administered prior to, at the same time as, or subsequent to administration of DHA, or in some combination thereof.

Be emphasized that the term “kit of parts”, "combined preparation" or also called "juxtaposition" herein, means that the components of the combined preparation need not be present as an union (the components in the combination did not enter into direct interaction with each other), for example in a composition, to be available for use separately or sequentially. Thus, the term "juxtaposed" means that is not necessarily true combination, in view of the physical separation of the components.

USES OF THE COMPOSITIONS AND KIT OF PARTS OF THE INVENTION

A third aspect of the inventions refers to the composition or the kit of parts of the invention, for use in therapy or for use as a medicament or medicine.

The term "medicine" or “medicament” as used herein refers to any substance used for prevention, diagnosis, alleviation, treatment or cure of disease in man and/or animals.

A fourth aspect of the invention refers to the composition or the kit of parts of the invention, for its use in the treatment or amelioration of eye diseases.

In a preferred embodiment of the fourth aspect of the invention the eye disease is macular oedema due to wet macular degeneration, diabetes or inflammation. More preferably, for the treatment of macular oedema, the composition or the kit of parts of the invention comprises an antiangiogenic or a steroid as active ingredient.

In another preferred embodiment of the fourth aspect of the invention, the eye disease is the damage to photoreceptors and/or RPE cells. More preferably, the damage to photoreceptors and/or RPE cells is selected from the list consisting of dry macular degeneration, macular dystrophies, high myopia, diabetes, postoperative damage or any combination thereof.

As shown in examples of the present invention, the use of EPA and DHA in the indicated ratios and dosages, provides a particularly effective therapy for those conditions and avoids the side effects of other therapies if indicated.

In a preferred embodiment of the fourth aspect of the invention, the retinal dystrophies are selected from the list consisting of retinitis pigmentosa, rod-cone dystrophy, Best dystrophy, adult vitelliform dystrophy, or any combination thereof.

A particular embodiment of the fourth aspect of the invention refers to the composition or the kit of parts of the invention, for its use in the treatment of dry macular degeneration.

In another preferred embodiment of the fourth aspect of the invention, the eye disease is severe dry eyes (keratoconjunctivitis sicca or xerophthalmia).

The precise dosage of the further active ingredient will vary with the dosing schedule, the oral potency of the particular agent chosen, the age, size, sex and condition of the subject, the nature and severity of the disorder to be treated, and other relevant medical and physical factors.

The medicament of the invention or a composition comprising omega 3 fatty acids, preferably EPA and DHA , may advantageously be administered in a single daily dose, or the total daily dosage may be administered in doses of two, three or four times daily. Preferably, the EPA and DHA, or a salt or an ester thereof, is for administration once per day or twice per day.

In a more preferred embodiment, the pharmaceutical composition or kit of parts of the invention, or a composition or a kit of parts comprising omega 3 fatty acids, preferably eicosapentaenoic acid and docosahexaenoic acid, can be administered one or more times a day, for example, 1, 2, 3 or 4 times a day, in a typical total daily amount to be above 7 g per day of omega 3 fatty acids, more preferably to be above 8 g per day of omega 3 fatty acids, more preferably to be above 7 g per day of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and more preferably to be above 8 g per day. Preferably, the combined dosage is from 7.5g to 15 g per day. In a more preferred embodiment, the pharmaceutical composition or kit of parts of the invention can be administered in a dose wherein the combined EPA and DHA is such that the arachidonic acid/ eicosapentaenoic acid mass ratio in the blood is in the range of 0.8 to 3, and more preferably from 1 to 1.5.

A fifth aspect of the invention refers to the use of the food composition of the invention, for the treatment or amelioration of macular degeneration and retinal dystrophies.

In a preferred embodiment of the fifth aspect of the invention, the retinal dystrophies are selected from the list consisting on Retinitis pigmentosa, rod-cone dystrophy, Best dystrophy, adult vitelliform dystrophy, or any combination thereof.

A particular embodiment of the fifth aspect of the invention refers to the composition or the kit of parts of the invention, for its use in the treatment or amelioration of dry macular degeneration.

In a more preferred embodiment, the food composition of the invention, or a food composition comprising omega 3 fatty acids, preferably eicosapentaenoic acid and docosahexaenoic acid, can be administered one or more times a day, for example, 1, 2, 3 or 4 times a day, in a typical total daily amount to be above 7 g per day of omega 3 fatty acids, more preferably to be above 8 g per day of omega 3 fatty acids, more preferably to be above 7 g per day of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and more preferably to be above 8 g per day. Preferably, the combined dosage is from 7.5g to 15 g per day. In a more preferred embodiment, the pharmaceutical composition or kit of parts of the invention can be administered in a dose wherein the combined EPA and DHA is such that the arachidonic acid/ eicosapentaenoic acid mass ratio in the blood is in the range of 0.8 to 3 preferably between 1 to 1.5.

DEFINITIONS

As it used here, the terms "active ingredient", "active substance", "active pharmaceutical substance", "active principle" or "active pharmaceutical ingredient" means any component that potentially provides a pharmacological activity or another different effect in the diagnosis, cure, mitigation, treatment or prevention of a disease, or that affect the structure and function of the human body and of other animals. The term includes those components that promote a chemical change in the elaboration of the medicament and that are present in the same in a predicted modified form that provides the specific activity or the effect.

Either compositions of the present invention, as well as the kit of parts, can be formulated for its administration in an animal and more preferably in a mammal, including humans, in a variety of forms known in the state of the art. Therefore, they can be included, but not limited to, sterile aqueous solution or in biological fluids, such as serum. The aqueous solutions could be buffered or not and they can contain other active or inactive ingredients as well. The additional components include salts to modulate ionic strength, preservatives, including but not limited to, antimicrobial agents, antioxidants, chelating agents and similar, and nutrients including glucose, dextrose, vitamins and minerals. Alternatively, the compositions may be prepared for its administration in solid form. Compositions can be combined with other various vehicles or inert excipients, including but not limited to: agglutinating agent such as microcrystalline cellulose, tragacanth, gelatin; excipients such as starch or lactose; dispersant agents such as alginic acid of maize starch; lubricants such as magnesium stearate; gliding agents such as colloidal silicon dioxide; sweetener such as sucrose or saccharine; or aromatic agents such as mint or methyl salicylate.

The term "medicament", as it is used in this report, makes reference to any substance used for prevention, diagnosis, relief, treatment or cure of diseases in humans and animals. In the context of the present invention, the disease is macular degeneration and retinal dystrophies.

Such compositions or combined preparations and/or its formulations may be administered in an animal, including a mammal and therefore humans, in a variety of forms, including but not limited to, intraperitoneal, intravenous, intramuscular, subcutaneous, intrathecal, intraventricular, oral, enteral, parenteral, intranasal or topic.

The dose to obtain an amount therapeutically effective depends on a variety of factors, such as for instance, age, sex, weight, tolerance of the mammal. In the sense used in this description, the term "amount therapeutically effective" refers to the amount of omega 3

fatty acids, preferably eicosapentaenoic acid (EPA), and more preferably a combination of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), that produce the desired effect and in general it is determined among other factors, by the intrinsic characteristics of the prodrug, derivatives or analogs and by the therapeutic effect to be obtained. The "adjuvant" and "vehicles pharmaceutically acceptable" that could be used in such compositions are well known vehicles in the field.

As used in the specification and the appended claims the term "pharmaceutically acceptable carrier" is intended to include formulation used to stabilize, solubilize and otherwise be mixed with active ingredients to be administered to living animals, including humans. This includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. Except insofar as any conventional media or agent is incompatible with the active compound, such use in the compositions is contemplated.

The invention now will be described with respect to the following examples; however, the scope of the present invention is not intended to be limited thereby.

Examples

Method and Materials

Ten eyes of the macular retinal dystrophy eyes had Retinitis Pigmentosa (R.P), 2 eyes had Best disease, 2 eyes had Adult Vitelliform dystrophy and 2 eyes had Cone dystrophy. All eyes had reduced visual acuity and reduced field test. They were treated with omega 3 which consisted of purified ethyl esters rich in EPA (400mg) and DHA (200mg) per gram for the liquid formulation. The dosage used in this pilot study was 15ml to 20ml of liquid formulation providing approximately 5.0 g to 10 g of EPA and and DHA per day. The dosage was divided into two daily doses of 7.5 to 10ml each. The dose was adjusted so that the blood AA/EPA ratio was within 1 to 1.5 .The intraocular pressures an all eyes were well controlled with anti-glaucomatous drops.

Results

The visual acuity was recorded using the EDTRS electronic chart at 6 weeks and 3 months. Visual field testing was also recorded with a field testing machine (Zeiss, Humphreys).

Fig. 2 shows the number of lines gained and the number of eyes over the study period. Patients taking 8-10g day had 12.85 letters gain at 6 months and patients taking 5g/day had 10.57 letters gain at 6 months. Average gain is 11.85 letters at 6 months. In all cases the visual field testing has improved.

The Fig 3 shows the number of letters gained according to the AA/EPA ratio of each eye. Patients with a ratio between 1 and 1.50 had 15.67 letters gained. Patients with a ratio of 1.51 to 1.99 had 11.11 letters gained and patients with >2 ratio had 7.94 letters gained.

Conclusion

The pilot study indicates that high-dose omega-3 fatty acids (5 to 10 grams of EPA and DHA per day) represents a potentially new therapeutic approach for the treatment of macular dystrophies and dry macular degeneration. The dose of each patient should be adjusted so that the AA/EPA is between 1 to 1.50 to have the maximum clinical benefit.

The examples show that it can achieve more visual acuity gain when the AA/EPA ratio is between 1 and 1.50 than when it is higher. There is no previous art to show that the AA/EPA ratio can be used to adjust the EPA and DHA dosage to be able to achieve maximal visual acuity gain in these eye pathologies in which the rods/cones/retinal pigment epithelium cells are damaged.

Claims

1. A composition comprising at least 7 g of an omega 3 fatty acid, for use in the treatment or amelioration of eye disease.

2. A kit of parts comprising at least 7 g of an omega 3 fatty acid, for use in the treatment, of eye diseases.

3. The composition according to claim 1 or the kit of parts according to claim 2, comprising at least 7.5 g of an omega 3 fatty acid.

4. The composition or the kit of parts according to any one of claims 1-4, comprising at least 8 g of an omega 3 fatty acid.

5. The composition according to claim 1 or the kit of parts according to claim 2, comprising from 8 g to 10 g of omega 3 fatty acids.

6. The composition or the kit of parts according to any one of claims 1-5, comprising at least 30 weight % omega-3 fatty acid, preferably at least 50 weight % omega-3 fatty acid.

7. The composition or the kit of parts according to any one of claims 1-6, wherein the omega 3 fatty acid is selected from the list consisting of: eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), alpha liniolenic acid (ALA), stearidonic acid (SA), oeicosatetraenoic acid, or any combination thereof.

8. The composition or the kit of parts according to any one of claims 1-7, wherein the omega 3 fatty acid is eicosapentaenoic acid.

9. The composition or the kit of parts according to any one of claims 1-8, comprising eicosapentaenoic acid and docosahexaenoic acid.

10. The composition or the kit of parts according to any one of claims 1-9, comprising eicosapentaenoic acid and docosahexaenoic acid in a mass ratio from 1:1 to 5:1.

11. The composition or the kit of parts according to any one of claims 1-10 comprising eicosapentaenoic acid and docosahexaenoic acid in a mass ratio of about 2:1.

12. The composition or the kit of parts according to any one of claims 1-11, wherein the composition is a pharmaceutical composition or the kit of part is a pharmaceutical kit of parts.

13. The composition or the kit of parts according to any one of claims 1-11, further comprising a pharmaceutically acceptable carrier.

14. The composition or the kit of parts according to any one of claims 1-11, wherein the composition is a food composition or the kit of part is a food kit of parts.

15. The composition or the kit of parts according to claim 14, further comprising another active ingredient or a food ingredient.

16. The composition or the kit of parts according to any one of claims 1-15, or a composition or kits of part comprising eicosapentaenoic acid and docosahexaenoic acid, wherein the amount of eicosapentaenoic acid and docosahexaenoic acid can be administered 1, 2, 3 or 4 times a day, in a typical total daily amount to be above of 7 g per day, and more preferably is comprised between 7.5 g to 10 g per day.

17. The composition or the kit of parts according to any one of claims 1-16, wherein the amount of eicosapentaenoic acid and docosahexaenoic acid is such that the arachidonic acid/ eicosapentaenoic acid mass ratio in the blood is in the range of 0.8 to 3, and preferably from 1 to 1.5.

18. The composition or the kit of parts according to any one of claims 1-17, wherein the eye disease is macular oedema due to wet macular degeneration, diabetes or inflammation.

19. The composition or the kit of parts according to claim 18, comprising an antiangiogenic or a steroid as active ingredient.

20. The composition or the kit of parts according to any one of claims 1-17, wherein the eye disease is the damage to photoreceptors and/or RPE cells.

21. The composition or the kit of parts according to claim 20, wherein the damage to photoreceptors and/or RPE cells is selected from the list consisting of dry macular

degeneration, macular dystrophies, high myopia, diabetes, postoperative damage or any combination thereof.

22. The composition or the kit of parts according to any one of claims 20-21, wherein the macular dystrophy is selected from the list consisting of retinitis pigmentosa, rod-cone dystrophy, best dystrophy, adult vitelliform dystrophy, or any combination thereof.

23. The composition or the kit of parts according to any one of claims 1-17, wherein the eye disease is xerophthalmia

AMENDED CLAIMS
received by the International Bureau on 27 January 2015 (27.01.2015)

1. A composition or a kit of parts comprising an omega-3 fatty acid in a total daily amount to be administered above of 7.5 g per day, for use in the treatment or amelioration of eye disease in a human, wherein the omega 3 fatty acid is eicosapentaenoic acid (EPA), and wherein the arachidonic acid/ eicosapentaenoic acid mass ratio in the blood of the human is maintained in the range of 0.8 to 3.

2. The composition or the kit of parts according to claim 1, wherein the omega 3 fatty acids to be administered above of 7.5 g per day are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

3. The composition or the kit of parts according to any one of claims 1-2, wherein the arachidonic acid/ eicosapentaenoic acid mass ratio in the blood of the human is maintained in the range of 1 to 1.5.

4. The composition or the kit of parts according to any one of claims 1-3, wherein the eicosapentaenoic acid and docosahexaenoic acid are in a mass ratio from 1:1 to 5:1.

5. The composition or the kit of parts according to any one of claims 1-4, wherein the eicosapentaenoic acid and docosahexaenoic acid are in a mass ratio of about 2:1.

6. The composition or the kit of parts according to any one of claims 1-5, wherein the eicosapentaenoic acid and docosahexaenoic acid are administered in a typical total daily amount comprised between 8 g to 10 g per day.

7. The composition or the kit of parts according to any one of claims 1-6, wherein the composition is a pharmaceutical composition or the kit of part is a pharmaceutical kit of parts.

8. The composition or the kit of parts according to claim 7, further comprising a pharmaceutically acceptable carrier.

9. The composition or the kit of parts according to any one of claims 7-8, further comprising another active ingredient.

10. The composition or the kit of parts according to any one of claims 1-6, wherein the composition is a food composition or the kit of part is a food kit of parts.

11. The composition or the kit of parts according to claim 10, further comprising another food ingredient.

12. The composition or the kit of parts according to any one of claims 1-11, wherein eye disease is macular oedema.

13. The composition or the kit of parts according to claim 12, wherein the macular oedema due to wet macular degeneration, diabetes or inflammation.

14. The composition or the kit of parts according to claim 13, comprising an antiangiogenic or a steroid as active ingredient

15. The composition or the kit of parts according to any one of claims 1-11, wherein eye disease is the damage to photoreceptors and/or RPE cells.

16. The composition or the kit of parts according to claim 14, wherein the damage to photoreceptors and/or RPE cells is selected from the list consisting of dry macular degeneration, macular dystrophies, high myopia, diabetes, postoperative damage or any combination thereof.

17. The composition or the kit of parts according to any one of claims 14-15, wherein the macular dystrophy is selected from the list consisting of retinitis pigmentosa, rod-cone dystrophy, best dystrophy, adult vitelliform dystrophy, or any combination thereof.

18. The composition or the kit of parts according to any one of claims 1-11, wherein the eye disease is xerophthalmia.

STATEMENT UNDER ARTICLE 19 (1)

After the issue of the International Search Report in the PCT/EP2014/058709, we proceed to submit these WRITTEN REPLAY and AMENDMENTS which will enable us to clarify the issues raised in the Written Opinion, all this under the PCt.

Reasoned statement with regard to novelty and inventive step; citations and explanations supporting such statement.

1. Amendments

In response to the Written Opinion of the International Preliminary Examination Authority,regarding the referenced application, we herein attach a new set of claims which shall constitute the basis for continuing the present examination before the IPEA.

This new set of claims finds explicit support as follows:

New claim	Basis
1	Orig. claims 1+3+16+17+pag.6 lin.27-29
2	Orig. claims 1+3+16+17+pag.6 lin.27-29
3	Orig. claims 1+3+16+17+pag.6 lin.27-29
4	Orig. claims 1+3+10 +16+17+pag.6 lin.27-29
5	Orig. claims 1+3+11+16+17+pag.6 lin.27-29
6	Orig. claims 1+3+10+11+16+17+pag.6 lin.27-29+examples
7	Orig. claims 1+3+10+11+12+16+17+pag.6 lin.27-29+examples
8	Orig. claims 1+3+10+11+12+13+16+17+pag.6 lin.27-29+examples
9	Orig. claims 1+3+10+11+12+13+15+16+17+pag.6 lin.27-29+examples
10	Orig. claims 1+3+10+11+14+16+17+pag.6 lin.27-29+examples
11	Orig. claims 1+3+10+11+14+15+16+17+pag.6 lin.27-29+examples
12	Orig. claims 1+3+10+11+12+13+14+15+16+17+18 +pag.6 lin.27-29+examples
13	Orig. claims 1+3+10+11+12+13+14+15+16+17+18 +pag.6 lin.27-29+examples
14	Orig. claims 1+3+10+11+12+13+14+15+16+17+18 +19+pag.6 lin.27-29+examples
15	Orig. claims 1+3+10+11+12+13+14+15+16+17+18 +20+pag.6 lin.27-29+examples
16	Orig. claims 1+3+10+11+12+13+14+15+16+17+18 +20+21+22+ pag.6 lin.27-29+examples
18	Orig. claims 1+3+10+11+12+13+14+15+16+17+18 +23+pag.6 lin.27-29+examples

2. Lack of novelty objections

The Examiner cites two documents in the International Search Report, namely documents **D1** (WO 2013/037794) and **D2** (WO 2010/118761), as relevant in terms of novelty and inventive step.

According to the Written Opinion, document **D1** does not affect the novelty of original claims 14-17, and document **D2** does not affect the novelty of claims 8, 10-11 and 16-19. None of the documents affect the original claims 16 and 17. The new enclosed claim 1 has been amended so that the product (composition or kit of parts) of the invention include the technical characteristics of the original claim 16 and 17.

Consequently, the new enclosed claim 1 is novel in light of **D1** and **D2** disclosure. The dependent claims 2 to 16 are novel and inventive by virtue of being dependent on claim 1.

3. Lack of inventive step objections

The main difference between new independent claim 1 and documents **D1** and/or **D2**, taken as the closest prior art, is that this documents fails to specifically address the use of omega-3 fatty acids in an specific dosage (at least 7.5 g of EPA per day and an EPA/AA ratio of 0.8 to 3, preferably 1 to 1.5), for use in the treatment or amelioration of an eye disease, in humans.

The technical effect associated with the choice of EPA and DHA dosage and EPA/AA ratio can be clearly found in the examples and figures of the patent application.

Consequently, since none of the documents mentioned refers to this combination of technical features, the skilled person would not consider with a reasonable expectation of success the use of the composition or kit of parts of new amended claim 1 for the treatment of an eye disease.

Therefore, the new set of claims attached herein should be considered inventive.

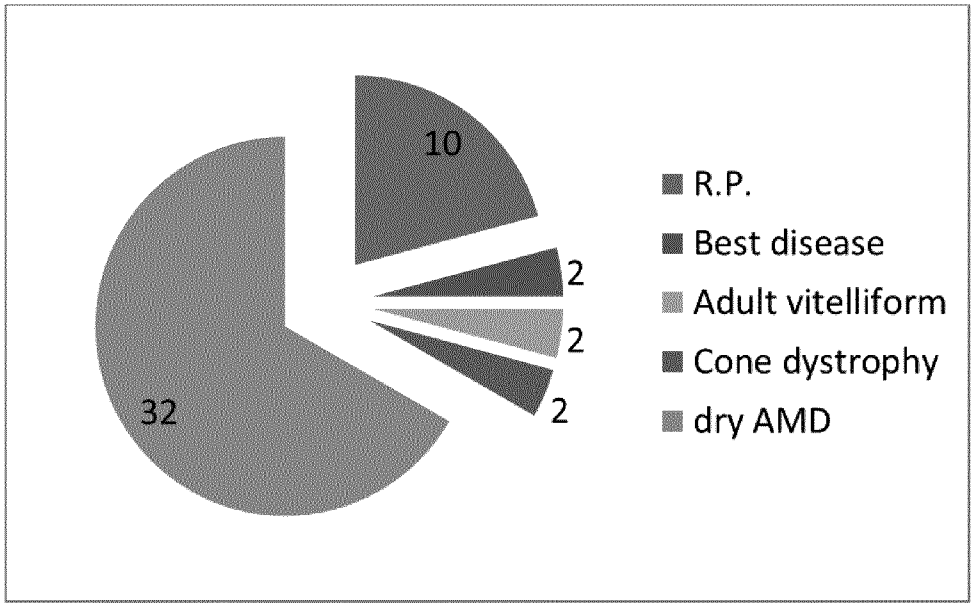
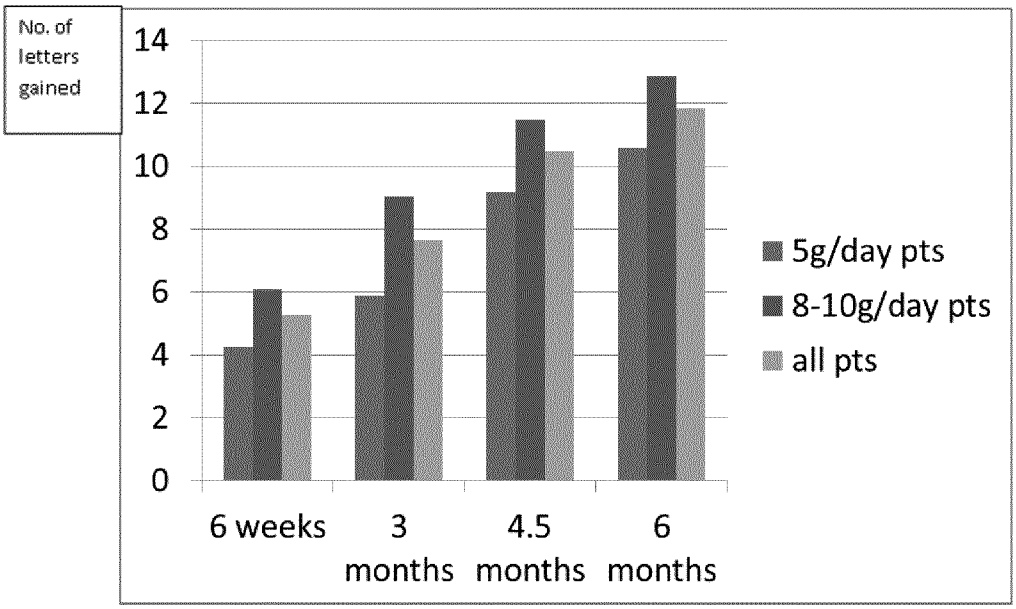

10
2
2
2
32
R.P.
Best disease
Adult vitelliform
Cone dystrophy
dry AMD

Fig. 1


No. of letters gained
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12
10
8
6
4
2
0
6 weeks
3 months
4.5 months
6 months
5g/day pts
8-10g/day pts
all pts

Fig. 2

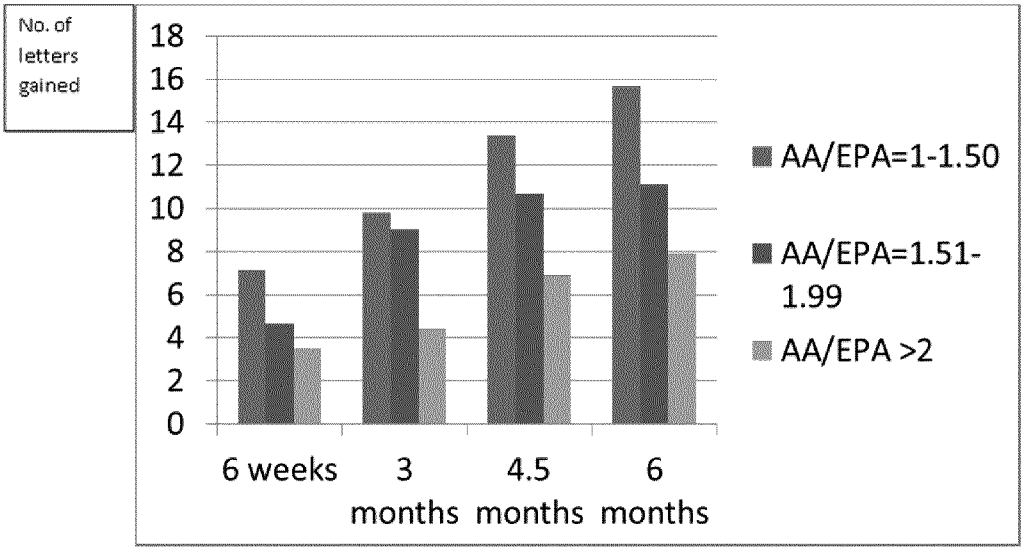
No. of letters gained
18
16
14
12
10
8
6
4
2
0
6 weeks
3 months
4.5 months
6 months
AA/EPA=1-1.50
AA/EPA=1.51-1.99
AA/EPA >2

Fig. 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/058709

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/202 A61P27/02 A61K45/06 A23L1/30
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P A23L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013/037794 A1 (GEORGIOU TASSOS [CY])	1-13,
	21 March 2013 (2013-03-21)	18-23
Y	page 6; claims 1, 10, 14, 17; table 1	1-23

X	WO 2010/118761 A1 (EOLAS SCIENCE LTD [IE];	1-7,9,
	CELA LOPEZ JOSE MANUEL [IE])	12-15,
	21 October 2010 (2010-10-21)	20-23
Y	claims 19, 21,23-24 26; examples 7, 8	1-23

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
3 September 2014	12/09/2014

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2014/058709

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