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(71) Applicant (for all designated States except US): **F. HOFFMANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse 124, CH-4070 Basel (CH).

(71) Applicant (for US only): **HOFFMANN-LA ROCHE INC.** [US/US]; 340 Kingsland Street, Nutley, New Jersey 07110 (US).

(72) Inventors: **CHAPUT, Evelyne**; 7, rue de Monenberg, F-68510 Sierentz (FR). **NIESOR, Eric J.**; Chemin de Bonmont 13c, CH-1260 Nyon (CH).

(74) Agent: **SCHIRLIN, Julien**; F. Hoffmann-La Roche AG, Grenzacherstrasse 124, CH-4070 Basel (CH).

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(54) Title: CETP MODULATOR FOR USE IN THE TREATMENT OF EYE DISEASE

(57) Abstract: The present invention relates CETP modulator which is useful in the prevention, treatment, delaying progression and/or reduction of eye diseases.



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CETP MODULATOR FOR USE IN THE TREATMENT OF EYE DISEASE

- The present invention relates CETP modulators which are useful in the prevention, treatment, delaying progression and /or reduction of eye diseases such as cataract, corneal clouding (opacification), glaucoma, uveitis, intraocular neovascular diseases, in particular proliferative retinopathies, Choroidal Neovascularization (CNV), diabetic and other ischemia-related
- 5 retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization, age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD and its method of preventing, retarding and ameliorating eye disease, such as cataract, corneal clouding (opacification), glaucoma, uveitis, intraocular neovascular
- 10 diseases, in particular proliferative retinopathies, choroidal neovascularization (CNV), diabetic and other ischemia-related retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization, age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD..
- 15 In another embodiment, the invention comprises a CETP modulator for use as therapeutic active substances for the prevention, the treatment, the prophylaxis and /or reduction of eye diseases such as cataract, corneal clouding (opacification), glaucoma, uveitis, intraocular neovascular diseases, in particular proliferative retinopathies, choroidal neovascularization (CNV), diabetic and other ischemia-related retinopathies, diabetic macular edema, pathological myopia, von
- 20 Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization, age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD.

In a particular embodiment, the present invention comprises a pharmaceutical composition comprising the CETP modulator, in particular 5-[2-([1-(2-ethylbutyl)cyclohexyl]carbonyl)amino]phenyl] 2-methylpropanethioate, and crospovidone (in

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particular crospovidone micronized), useful for the prevention, treatment, delaying progression, and/or reduction of eye diseases, such as cataract, corneal clouding (opacification), glaucoma, uveitis, intraocular neovascular diseases, in particular proliferative retinopathies, choroidal neovascularization (CNV), diabetic and other ischemia-related retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization, age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD. .

In another embodiment of the present invention relates to composition comprising a CETP modulator, in association with one or more carotenoid(s), in particular wherein the carotenoids are selected from xanthophylls, more particular wherein one carotenoid is lutein, most particularly wherein the carotenoids are lutein and one stereoisomer of zeaxanthin (more particularly zeaxanthin), useful for the prevention, treatment, delaying progression, and/or reduction of eye diseases, such as cataract, corneal clouding (opacification), glaucoma, uveitis, intraocular neovascular diseases, in particular proliferative retinopathies, choroidal neovascularization (CNV), diabetic and other ischemia-related retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization, age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD. Said composition is a nutraceutical composition or a pharmaceutical composition useful in particular for the prevention, treatment, delaying progression, and/or reduction eye diseases such as cataract, corneal clouding (opacification), glaucoma, uveitis, intraocular neovascular diseases, in particular proliferative retinopathies, choroidal neovascularization (CNV), diabetic and other ischemia-related retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization, age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD.

In a particular embodiment according to the invention the eyes diseases are cataract, corneal clouding (opacification), age-related macular degeneration (AMD), in particular AMD.

Brief description of the figures:

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Figure 1: Effect of Dalcetrapib (Dal) on plasma & liver lutein & zeaxanthin levels in hamsters fed FLORAGLO study a.

Figure 2: Effect of Dalcetrapib (Dal) on eyecups lutein & zeaxanthin levels in hamsters fed FLORAGLO study a.

- 5 Figure 3: Effect of Dalcetrapib (Dal) & Anacetrapib (Ana) on plasma & liver lutein & zeaxanthin levels in hamsters fed FLORAGLO study b.

The carotenoids are naturally-occurring compounds that have antioxidant properties. The carotenoids are common compounds synthesized by plants, and contribute greatly to the colouring of plants and some animals. The large majority of animal species of including
10 mammals, are unable to synthesize carotenoids *de novo* and accordingly rely upon diet to provide carotenoid requirements. Mammals also have a limited ability to modify carotenoids. A mammal can convert beta-carotene to vitamin A, but most other carotenoids are deposited in mammalian tissue in unchanged form. With respect to humans, about ten carotenoids are found in human serum. The major carotenoids in human serum are beta-carotene, alpha-carotene,
15 cryptoxanthin, lycopene and lutein. Small amounts of zeaxanthin, phytofluene, and phytoene are found in human organs.

Plasma lycopene, lutein and beta-carotene are the most powerful antioxidants for explaining the concentration of oxidatively modified LDL in human serum (Karppi J et al. *Atherosclerosis* 2010 April;209(2):565). In the participants in the observational Atherosclerosis Risk in Communities
20 (ARIC) study cohort patients were selected on the basis of B-mode carotid artery ultrasonograms were 231 asymptomatic age-, sex-, race-, and field center-matched case-control pairs. After adjustment for potential confounders, only the inverse association of lutein plus zeaxanthin with asymptomatic atherosclerosis was maintained. This study supports a modest inverse association between circulating levels of some carotenoids, particularly lutein plus zeaxanthin, and carotid
25 intima-media thickness (IMT) (Iribarren C et al. *Arterioscler Thromb Vasc Biol* 1997 June;17(6):1171). Dwyer et al Dwyer et al, *Circulation* 2001, 103(24), 2922) assessed the protective effects of the oxygenated carotenoid on progression of IMT of the common carotid arteries determined ultrasonographically and concluded that increased dietary intake of lutein is

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protective against the development of early atherosclerosis. These findings suggest that these carotenoid compounds may be important in early stages of atherosclerosis. Pre-incubation of human aortic endothelial cells with beta-carotene, lutein and lycopene significantly reduced VCAM-1 expression by 29, 28, and 13%, respectively. Pre-incubation with beta-carotene and lutein significantly reduced E-selectin expression by 38 and 34%, respectively. Pre-treatment with beta-carotene, lutein and lycopene significantly reduced the expression of ICAM-1 by 11, 14, and 18%, respectively (Martin KR et al, *Atherosclerosis* 2000 June;150(2):265). Patients with CVD tend to have lower plasma levels of carotenoids (Lidebjer C et al, *Nutr Metab Cardiovasc Dis* 2007 July;17(6):448).

- 10 Low levels of antioxidant carotenoids have been observed in subjects with mild cognitive impairment and with Alzheimer's disease by Rinaldi et al (Rinaldi P et al *Neurobiol Aging* 2003 November;24(7):915). Indeed, Xanthophyll such as lutein and zeaxanthin can cross the blood-retina barrier to preferentially accumulate in the macular region of the neural retina. They also accumulate in brain tissue. Recently Vishwanathan correlated the retinal levels of xanthophylls with those measured in the cerebellum and frontal cortex (Vishwanathan R et al, *Nutr Neurosci* 2013, 16(1), 21-).

- Of the ten carotenoids found in human serum, only two, trans- and/or meso-zeaxanthin and lutein, have been found in the human retina. Zeaxanthin is the predominant carotenoid in the central macula or foveal region and is concentrated in the cone cells in the centre of the retina, i.e., the fovea. Lutein is predominantly located in the peripheral retina in the rod cells. Therefore, the eye preferentially assimilates zeaxanthin over lutein in the central macula which is a more effective singlet oxygen scavenger than lutein. It has been theorized that zeaxanthin and lutein are concentrated in the retina because of their ability to quench singlet oxygen and scavenge free radicals, and thereby limit or prevent photic damage to the retina.

- 25 It is known that the carotenoids other than zeaxanthin and lutein that do enter the retina may cause adverse effects, such as the formation of crystalline deposits by canthaxanthin, which may take several years to dissolve. Canthaxanthin in the retina also causes a decreased adaptation to the dark.

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Vitamins (A, E or C), zinc, selenium, anthocyanins or macular pigments, such as, for example, lutein and zeaxanthin are usually used for their antioxidant properties. Lutein and zeaxanthin are macular pigments representing 99% of total pigments of the macula, which belong to the family of carotenoids, and specifically to the family of xanthophylls. Both pigments may exhibit on one
5 hand an indirect protective antioxidant effect through their capacity to absorb blue light particularly aggressive for photoreceptor and on the other hand direct radical scavenging antioxidant properties. US2005/0032914, US2010/0159029 and W02009/129859 describe compositions for oral administration, comprising lutein and zeaxanthin in combination with other non-enzymatic antioxidant products, for enhancing visual performance, inhibiting macular
10 degeneration or promoting eye health. US2007 /265351 describes a xanthophyll composition comprising lutein and zeaxanthin useful for eye health.

Moreover, lutein is defined by the Afssa (Agence Francaise de Securite Sanitaire des Aliments) as "an agent which contributes to protect retina and lens against oxidation" (Saisine n°2003-SA-0205, 2004) and scientific studies have shown a relationship between the dietary intake of
15 lutein/zeaxanthin and the likelihood of having AMD (SanGiovanni et al., AREDS report n°22, Arch Ophthalmol, 2007).

Recently, it has been demonstrated that aging eyes have a decreased amount of carotenoids deposited on the foveal region of the retina. Clinical and laboratory studies indicate that photic injury is at least one cause of age-related macular degeneration because of the cumulative effect
20 of repeated photic insult which leads to a gradual loss of photoreceptor cells and degeneration of macular tissue.

Age-related macular degeneration (AMD) is an irreversible blinding disease of the retina. Unlike cataracts which can be restored by replacing of the diseased lens, age-related macular degeneration cannot be treated by replacing the diseased retina because the retina is a component
25 of the central nervous system. Therefore, because no treatment for this disease exists once the photoreceptors are destroyed, prevention is the most efficient way to address age-related macular degeneration. Presently, prevention of age-related macular degeneration resides in limiting or preventing light and oxygen-induced (i.e., free radical-induced) damage to the retina because the retina is the only organ that is continuously exposed to high levels of light in a highly-
30 oxygenated environment.

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AMD is a leading cause of severe, irreversible vision loss among the elderly (Bressler, JAMA 291:1900-1 (2004)). It is characterized by a broad spectrum of clinical and pathologic findings, such as pale yellow spots known as drusen, disruption of the retinal pigment epithelium (RPE), choroidal neovascularization (CNV), and disciform macular degeneration. The manifestations of the disease are classified into two forms: non exudative (dry) and exudative (wet or neovascular). Drusen are the characteristic lesions of the dry form, and neovascularization characterizes the wet form. Disciform AMD is the fibrotic stage of the neovascular lesion.

There is a dramatic increase in the prevalence of AMD with advancing age. See, e.g. Leibowitz et al., *Surv Ophthalmol* 24(Suppl):335-610 (1980) and Klein et al., *Ophthalmology* 99:933-43 (1992). Although the wet form of AMD is much less common, it is responsible for 80%-90% of the severe visual loss associated with AMD (Ferris et al., *Arch Ophthalmol* 102:1640-2 (1984)). There is an estimated 1-1.2 million prevalent cases of wet AMD. The cause of AMD is unknown; however, it is clear that the risk of developing AMD increases with advancing age. Other known risk factors include family history and cigarette smoking. Postulated risk factors also include oxidative stress, diabetes, alcohol intake, and sunlight exposure. D'Amico, *N Engl J Med* 331:95-106 (1994) and Christen et al., *JAMA* 276:1147-51 (1996).

Dry AMD is characterized by changes in the RPE and Bruch's membrane. It is thought that the RPE, compromised by age and other risk factors, deposits lipofuscin and cellular debris on Bruch's membrane. These changes may be seen ophthalmoscopically as drusen, which are scattered throughout the macula and posterior retinal pole. There are also variable degrees of atrophy and pigmentation of the RPE. Dry AMD may be asymptomatic or accompanied by variable and usually minimal visual loss and is considered to be a prelude to development of wet AMD.

Wet AMD is typically characterized by CNV of the macular region. The choroidal capillaries proliferate and penetrate Bruch's membrane to reach the RPE and may extend into the subretinal space. The increased permeability of the newly formed capillaries leads to accumulation of serous fluid or blood under the RPE and/or the neurosensory retina or within the neurosensory retina. When the fovea becomes swollen or detached, decreases in vision occur. Fibrous metaplasia and organization may ensue, resulting in an elevated subretinal mass called a

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disciform scar that constitutes end-stage AMD and is associated with permanent vision loss (D'Amico DJ. N Engl J Med 331:95-106 (1994)). The neovascularization in AMD can be classified into different patterns based on fluorescein angiography of subfoveal choroidal neovascular lesions. TAP and VIP Study Groups, Arch Ophthalmol 121:1253-68 (2003). The
5 major angiographic patterns are termed classic and occult and are associated with different degrees of aggressiveness, vision losses, and response to different treatment options.

The group of xanthophylls includes (among many other compounds) lutein, zeaxanthin, neoxanthin, violaxanthin, and α - and β -cryptoxanthin. The latter compound is the only known xanthophyll to contain a beta-ionone ring, and thus β -cryptoxanthin is the only xanthophyll that
10 is known to possess pro-vitamin A activity for mammals. Even then, it is a vitamin only for plant-eating mammals that possess the enzyme to make retinal from carotenoids that contain beta-ionone (some carnivores lack this enzyme). In species other than mammals, certain xanthophylls may be converted to hydroxylated retinal-analogues that function directly in vision. For example, with the exception of certain flies, most insects use the xanthophyll derived R-
15 isomer of 3-hydroxyretinal for visual activities, which means that β -cryptoxanthin and other xanthophylls (such as lutein and zeaxanthin) may function as forms of visual "vitamin A" for them, while carotenes (such as beta carotene) do not.

In humans according to Kaplan et al. (*Clin Physiol Biochem* 1990, 8, 1) and Schmitz et al. (*J Nutr* 1991, 121, 1613) lutein and zeaxanthin are accumulated in lipophilic tissues and are carried
20 out by the lipoproteins.

Intestinal absorption and tissue distribution of carotenoids. Most likely because of their lipophilicity the absorption and distribution of carotenoids is complex and highly variable (Castenmiller, J.J. *Annu Rev Nutr* 1998;18:19). It involves intestinal components bile acids, enzymes such as esterase, receptors in enterocytes and inclusion into lipoproteins, secretion in
25 the plasma or lymph and distribution among lipoproteins and delivery to tissues. Greene et al (Greene, C.M. *Nutr Metab (Lond)* 2006;3:-6) noticed a relationship between lutein and zeaxanthin plasma concentration and HDL size and speculated that because of their location at the surface of lipoproteins these carotenoids could exchange during particle remodeling while HDL interact with other lipoproteins. In addition, genetic variation is involved in the inter-

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individual variability in carotenoid bioavailability as reviewed by Borel (Borel P, *Mol Nutr Food Res* 2012 February;56(2):228) who suggests a personalized dietary guideline for carotenoids according to individual genetic characteristics. Several attempts to increase the bioavailability of lutein with various formulations have been published. Although the availability from egg seems
5 satisfactory the simultaneous increase in plasma cholesterol may not be appropriate in a number of patients (Thurnham, D.I. *Nutr Res Rev* 2007 December;20(2):163).

Specific role of ABCA1 and pre-beta HDL in intestinal absorption. A first animal model of HDL deficiency syndrome has been described in chicken having a Z-linked mutation (Poernama, F. *J Lipid Res* 1990 June;31(6):955) later on found to affect ABCA1 function. Attie et al (Attie,
10 A.D. *J Lipid Res* 2002 October;43(10):1610} identified the E89K mutation in the ABCA1 gene of the WHAM chicken and this animal model provided the direct demonstration that ABCA1 regulates efflux of cholesterol from the basolateral surface of the enterocyte to pre-beta/poorly lipidated ApoA1 (Mulligan, J.D. *J Biol Chem* 2003 April 11;278(15):13356). The role of pre-beta HDL is very likely the rate limiting step in xanthophyll uptake at the intestinal level since
15 injection of mature HDL does not compensate for the absence of native poorly lipidated apoA1 (Mulligan, J.D. *J Biol Chem* 2003 April 11;278(15):13356). We hypothesized that HDL efficiently remodeled into pre-beta HDL by CETP activity (Niesor, E.J. 2010 *J Lipid Res* 2010 December;51(12):3443) is involved in the process of intestinal lipidation of native HDL by enterocyte and that trace amounts of sterols of plant origin (phytosterols) are also taken-up by
20 this process (Niesor, E.J. *Atherosclerosis* 2011 December;219(2):761). We have previously shown that CETP is a major component of HDL remodeling and pre-beta-HDL formation in human plasma and that CETP modulators such as Dalcetrapib can enhance CETP activity involved in HDL remodeling (Niesor, E.J. 2010 *J Lipid Res* 2010 December; 51(12):3443). This will lead to an increase in pre-beta HDL formation in plasma, lipidation by the basolateral
25 ABCA1 of enterocytes and eventually increase carotenoid absorption. This phenomenon was not observed with non-selective/complete CETP inhibitors such as torcetrapib. The same increase in pre-beta HDL occurring at the retinal level may increase the efflux of excess cholesterol and oxidized lipids as described by Ishida et al (Ishida, B.Y. *Br J Ophthalmol* 2006 May;90(5):616).

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It has been found according to the present invention that not all CETP inhibitors are useful in increasing plasma and tissue xanthophylls for the prevention, treatment and or reduction delaying progression and /or reduction eye diseases such as cataract, corneal clouding (opacification), glaucoma, uveitis, intraocular neovascular diseases, in particular proliferative
5 retinopathies, choroidal neovascularization (CNV), diabetic and other ischemia-related retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization, age-related macular degeneration (AMD. CETP modulator such as S-[2-[1-(2-ethylbutyl)cyclohexylcarbonylamino]-phenyl]2-methylthiopropionate are useful in the
10 prevention, treatment and/or reduction of eye diseases in particularly AMD. .

It was indeed proven that CETP inhibitors from two different chemical classes have been developed and reached late stage clinical development. The first class are potent CETP inhibitors which are 3,5-bis-trifluoromethyl-benzene derivatives such as torcetrapib (Clark RW, . Arterioscler Thromb Vasc Biol. 2004;24(3):490-7) and anacetrapib that have been shown to raise
15 plasma HDL-C by up to 130% in humans ((Krishna R, Clin Pharmacol Ther. 2008 Dec;84(6):679-83.)). The phase III mortality/morbidity study of torcetrapib was terminated prematurely due to increased CV and non-CV deaths and events, due to off-target effects (Barter PJ, N Engl J Med. 2007;357(21):2109-22) unrelated to CETP inhibition (Forrest MJ, Br J Pharmacol. 2008;154(7):1465-73., Hu X, Endocrinology. 2009;150(5):2211-9.). The second
20 chemical class are "CETP modulator" such as benzenethiol derivatives, represented by S-[2-[1-(2-ethylbutyl)cyclohexylcarbonylamino]-phenyl] 2-methylthiopropionate which raises HDL-C by up to 36% in humans at the dose of 600mg (Stein EA, Am J Cardiol. 2009;104(1):82-91.) and was stopped in a phase III outcome study due to inefficacy for CVD patient.

In addition to potency, the mechanism of CETP inhibition by compounds derived from the two
25 chemical classes is also likely to be different. The binding of torcetrapib to CETP increases its affinity for lipoproteins and induces the formation of an inactive high affinity complex between CETP and lipoproteins such as HDL (Clark RW, J Lipid Res 2006;47: 537-552). The CETP-lipoprotein complex, similar to the one induced by the CETP inhibitor antibody TP2 (Swenson TL, J Biol Chem 1989; 264:14318-26.) cannot efficiently exchange neutral lipid between
30 different lipoprotein particles. Although the exact mechanism by which the CETP modulator

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such as S-[2-[1-(2-ethylbutyl)cyclohexylcarbonylamino]-phenyl] 2-methylthiopropionate decreases CETP activity has not been elucidated, the mode of action has been suggested to involve the direct specific interaction between cysteine 13 (Cys13) of CETP and benzenethiol moiety of 1-(2-Ethyl-butyl)-cyclohexanecarboxylic acid (2-mercapto-phenyl)-amide the active
5 metabolite of S-[2-[1-(2-ethylbutyl)cyclohexylcarbonylamino]-phenyl] 2-methylthiopropionate, which is cleaved by non specific esterases in the gastrointestinal tract and in plasma, thus allowing the formation of a disulphide bound with CETP (Okamoto H, Nature 2000; 406(6792):203–207).

It is of interest to distinguish between the two classes of compounds as it appears that they have
10 different mechanisms of action. Therefore there is a need to differentiate in vitro or ex vivo the CETP modulator such as S-[2-[1-(2-ethylbutyl)cyclohexylcarbonylamino]-phenyl] 2-methylthiopropionate, bis [2-[1-(2-ethylbutyl)cyclohexylcarbonylamino]phenyl] disulfide or 1-(2-Ethyl-butyl)-cyclohexanecarboxylic acid (2-mercapto-phenyl)-amide and its prodrug derivatives from all other CETP inhibitors, especially the potent CETP inhibitors such as 3,5-bis-
15 trifluoromethyl-benzene derivatives (i.e. torcetrapib and anacetrapib).

A CETP modulator is thus defined as a compound which decreases cholesteryl ester transfer activity of CETP AND increases CETP induced HDL remodelling leading to an enhanced level of pre-beta/nascent HDL particles (Niesor JLR and Maugeais et al BBA Lipids).

Unless otherwise stated, the following terms used in the specification and claims have the
20 meanings given below:

As used herein, the singulars forms “a”, “an”, and “the” include plural referents unless the contents clearly dictates otherwise. Therefore a compound optionally includes a combination of two or more such compound, and the like.

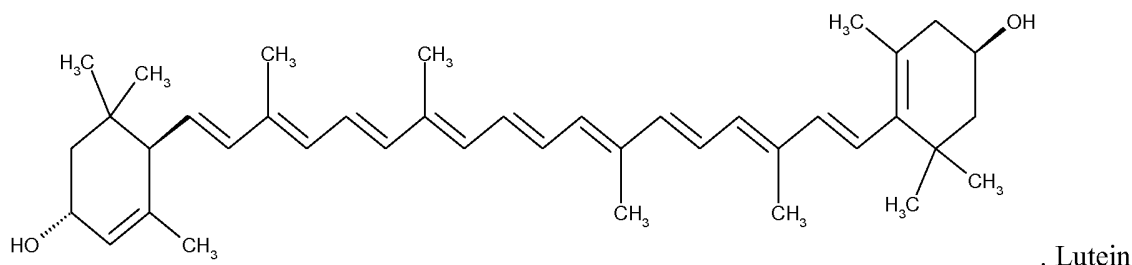
“CETP modulator ” refers to a compound which modulates CETP activity (assessed by
25 standard transfer assays) by inducing conformational changes of the CETP polypeptide once bound to the CETP polypeptide, wherein the conformational change is measured as hereunder described. Such specific interactions allow cholesteryl ester transfer activity of CETP to proceed between HDL particles AND increase CETP induced production of nascent pre-beta HDL.

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Preferably the CETP modulator refers to all compounds that would bind to cysteine 13 of the CETP polypeptide. More preferably, the “CETP modulator” is selected from S-[2-[1-(2-ethylbutyl)cyclohexylcarbonylamino]-phenyl] 2-methylthiopropionate, 1-(2-Ethyl-butyl)-cyclohexanecarboxylic acid (2-mercapto-phenyl)-amide and or bis [2-[1-(2-ethylbutyl)cyclohexylcarbonylamino]phenyl] disulfide. Most preferably, “CETP modulator” is S-[2-[1-(2-ethylbutyl)cyclohexylcarbonylamino]-phenyl]2-methylthiopropionate as a prodrug or 1-(2-Ethyl-butyl)-cyclohexanecarboxylic acid (2-mercapto-phenyl)-amide as its active metabolite.

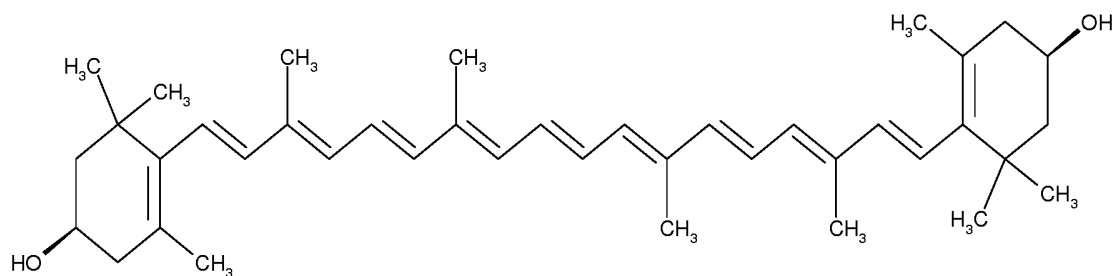
The term “diluent” refers to an excipient which fills out the size of a tablet or capsule, making it practical to produce and convenient for the consumer to use. Suitable diluents include e.g. pharmaceutically acceptable fillers, such as microcrystalline cellulose (e.g. Avicel[®]), crospovidone micronized, cellulose powder, lactose spray-dried, lactose anhydrous, lactose monohydrate, dibasic calcium phosphate, sugars, sugar alcohols, corn starch, starch, pregelatinized starch, colloidal silicon dioxide, polysaccharides, and mixtures thereof.

Lutein is synthesized by plants and found in high quantities in green leafy vegetables such as spinach and kale. Lutein chemical structure is :



(CAS registry number 127-40-2) is also known as (3*R*,3'*R*,6'*R*)-β,ε-Carotene-3,3'-diol,

Zeaxanthin (CAS registry number 144-68-3) also known as (3*R*,3'*R*)-β,β-Carotene-3,3'-diol has the following chemical structure:



Zeaxanthin is present in corn, saffron, wolfberries.

The term "effective amount" or "therapeutically effective amount" refers to an amount of a drug effective to treat a disease or disorder in a mammal. In the case of age-related macular degeneration (AMD), the effective amount of the drug can reduce or prevent vision loss. For AMD therapy, efficacy in vivo can, for example, be measured by one or more of the following: assessing the mean change in the best corrected visual acuity (BCVA) from baseline to a desired time, assessing the proportion of subjects who lose fewer than 15 letters in visual acuity at a desired time compared with baseline, assessing the proportion of subjects who gain greater than or equal to 15 letters in visual acuity at a desired time compared with baseline, assessing the proportion of subjects with a visual-acuity Snellen equivalent of 20/2000 or worse at desired time, assessing the NEI Visual Functioning Questionnaire, assessing the size of CNV and amount of leakage of CNV at a desired time, as assessed by fluorescein angiography, etc. A "therapeutic dose" is a dose which exhibits a therapeutic effect on the patient and a subtherapeutic dose is a dose which does not exhibit a therapeutic effect on the patient treated.

An "intraocular neovascular disease" is a disease characterized by ocular neovascularization. Examples of intraocular neovascular diseases include, but are not limited to, e.g., proliferative retinopathies, choroidal neovascularization (CNV), age-related macular degeneration (AMD), diabetic and other ischemia-related retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization, etc.

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The term "antibody" encompasses the various forms of antibody structures including but not being limited to whole antibodies and antibody fragments. The antibody according to the invention is preferably a humanized antibody, chimeric antibody, or further genetically engineered antibody as long as the antibody binds to an epitope of the CETP polypeptide

5 wherein the said epitope is only accessible (exposed) to the antibody either in the CETP:CETP modulator complex form or in the CETP native form.

"Antibody fragments" comprise a portion of a full length antibody, preferably the variable domain thereof, or at least the antigen binding site thereof. Examples of antibody fragments include diabodies, single-chain antibody molecules, and multispecific antibodies formed from antibody fragments. scFv antibodies are, e.g. described in Houston, J.S., Methods in Enzymol.
10 203 (1991) 46-96).

The terms "monoclonal antibody" as used herein refer to a preparation of antibody molecules of a single amino acid composition.

The term "epitope" includes any polypeptide determinant capable of specific binding to an antibody. In certain embodiments, epitope determinant includes chemically active surface
15 groupings of molecules such as amino acids, sugar side chains, phosphoryl, or sulfonyl, and, in certain embodiments, may have specific three dimensional structural characteristics, and or specific charge characteristics. An epitope is a region of an antigen that is bound by an antibody.

"CETP:CETP modulator complex" refers to the complexation of the CETP polypeptide with the CETP modulator as described herein. Preferably the "CETP:CETP modulator complex" results
20 from the contact of CETP polypeptide with a compound that binds to cysteine 13 or other free cysteines, preferably that binds to cysteine 13 of the CETP polypeptide as described herein.

The term "binding" or "bind to" refers to the specific association or other specific interaction between two molecular species, such as protein-protein or protein-small molecule interactions. It
25 is contemplated that such association is mediated through specific binding sites on each of the two interacting molecular species.

The term "binding site" refers to the reactive region or domain of a molecule that directly participates in its specific binding with another molecule. For example, when referring to the

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binding site on a protein, binding occurs as a result of the presence of specific amino acid sequence that interacts with the other molecule.

The term “hygroscopic polymeric excipient(s)” means polymeric excipient(s) which take(s) up moisture for example by absorption or adsorption even at relative humidity as low as 50%, at room temperature (e.g. about 25 °C). The moisture uptake is measured e.g by dynamic vapor sorption at room temperature. As an example the hygroscopicity can be measured in accordance with the method disclosed in the European Pharmacopoeia – 6th Edition (2008), Chapter 5.11. The dynamic vapor sorption technique measures the change in mass which is produced by varying the vapor concentration surrounding the product. Suitable “hygroscopic polymeric excipients” are hydroxypropyl methylcellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, hydroxyethylmethyl cellulose, carboxypolymethylene, methylcellulose, ethylcellulose, hydroxyethyl cellulose, celluloseacetate, polyvinylpyrrolidone crosslinked polyvinylpyrrolidone, micronized crosslinked polyvinylpyrrolidone, carboxymethylcellulose sodium, carboxymethylcellulose calcium, crosslinked carboxymethylcellulose, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powder, carboxymethyl starch, starch, pregelatinized starch or mixture thereof. In particular “hygroscopic polymeric excipients” refer to hydroxypropyl methylcellulose, carboxymethylcellulose sodium, microcrystalline cellulose and micronized crosslinked polyvinylpyrrolidone. Examples of “water insoluble hygroscopic polymers” at room temperature (e.g. about 25 °C) include low-substituted hydroxypropyl cellulose, carboxypolymethylene, ethylcellulose, celluloseacetate, crosslinked polyvinylpyrrolidone, micronized crosslinked polyvinylpyrrolidone, carboxymethylcellulose calcium, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powder, and starch.

The term “Super-disintegrant” refers to disintegrants that very rapidly expand upon contact with water. Generally speaking, superdisintegrants are disintegration agents which can be used in a fractional amount of normal disintegrants to obtain the same effect. Examples of superdisintegrants include cross-linked carboxymethyl cellulose sodium (a.k.a. croscarmellose sodium), sodium starch glycolate, and cross-linked polyvinyl pyrrolidone (a.k.a. crospovidone). Croscarmellose sodium is commercially available from FMC Corp. under the trade name Ac-Di-Sol® and from Avebe Corp. under the trade name Primellose®. Sodium starch glycolate is

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commercially available from Penwest Pharmaceuticals Co. under the tradename Explotab[®] and from Avebe Corp. under the tradename Primojel[®]. Crospovidone is commercially available from BASF Corp. under the tradename Kollidon[®] CL and from International Specialty Chemicals Corp. under the tradename Polyplasdone[®]. Croscarmellose is also commercially available from
5 Mingtai Chemical Co. Ltd under the tradename DISOLCEL[®] and from J. Rettenmaier & Söhne GmbH + Co (JRS) under the tradename Vivasol[®]. The most preferred superdisintegrants are croscarmellose sodium and crospovidone.

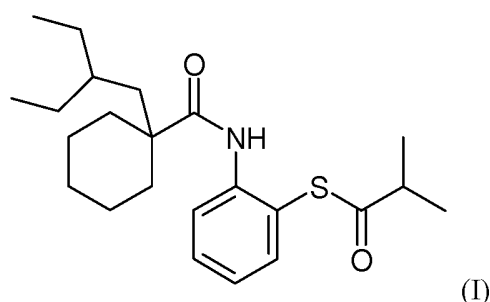
The term “water instable” means the presence of a hydrolysis sensitive functional group like an ester, amide or thioester.

- 10 In a particular embodiment of the invention, the present invention shows positive interaction of a combination of a CETP modulator with carotenoid(s), more particular with xanthophyll(s) such as lutein, trans-zeaxanthin, meso-zeaxanthin and astaxanthin either alone or in combination thereof in the prevention, treatment, delaying progression and /or reduction of eye diseases such as cataract, corneal clouding (opacification), glaucoma, uveitis, intraocular neovascular diseases,
15 in particular proliferative retinopathies, choroidal neovascularization (CNV), diabetic and other ischemia-related retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization, age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD..
- 20 In a particular embodiment of the invention, the present invention shows a synergy of a combination of a CETP modulator with carotenoid(s), more particular with xanthophyll(s) such as lutein, trans-zeaxanthin, meso-zeaxanthin and astaxanthin either alone or in combination thereof in the prevention, treatment, delaying progression and /or reduction of eye diseases such as cataract, corneal clouding (opacification), glaucoma, uveitis, intraocular neovascular diseases,
25 in particular proliferative retinopathies, choroidal neovascularization (CNV), diabetic and other ischemia-related retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization, age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD..

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Unless otherwise stated all percentages are given in weight percent of the total weight of the composition.

In a particular embodiment, the “CETP modulator” is thioisobutyric acid S-(2-{[1-(2-ethylbutyl)-cyclohexanecarbonyl]-amino}-phenyl) ester, also known as S-[2-([1-(2-ethylbutyl)-cyclohexyl]-carbonyl)amino]phenyl]2-methylpropanethioate, dalcetrapib or a compound of formula I



S-[2-([1-(2-ethylbutyl)cyclohexyl] carbonyl] amino) phenyl] 2- methylpropanethioate has been shown to be a modulator of CETP activity in humans (de Grooth et al., *Circulation*, 105, 2159-2165 (2002)) and rabbits (Shinkai et al., *J. Med. Chem.*, 43, 3566-3572 (2000); Kobayashi et al., *Atherosclerosis*, 162, 131-135 (2002); and Okamoto et al., *Nature*, 406 (13), 203-207 (2000)). S-[2-([1-(2-ethylbutyl) cyclohexyl] carbonyl] amino) phenyl] 2-methylpropanethioate has been shown to increase plasma HDL cholesterol in humans (de Grooth et al., *supra*) and in rabbits (Shinkai et al., *supra* ; Kobayashi et al., *supra* ; Okamoto et al., *supra*). Moreover, S-[2-([1-(2-ethylbutyl) cyclohexyl] carbonyl] amino) phenyl] 2-methylpropanethioate has been shown to decrease LDL cholesterol in humans (de Grooth et al. , *supra*) and rabbits (Okamoto et al., *supra*). S-[2-([1-(2-ethylbutyl)cyclohexyl] carbonyl] amino) phenyl] 2-methylpropanethioate, as well as methods of making and using the compound, are described in EP patent EP1020439, Shinkai et al., *J. Med. Chem.* 43:3566-3572 (2000) or WO 2007/051714, WO 2008/074677 or WO2011/000793.

In a preferred embodiment the CETP modulator (e.g. compound of formula I) is a solid in crystalline or amorphous form, more preferably in crystalline form. In a particular embodiment

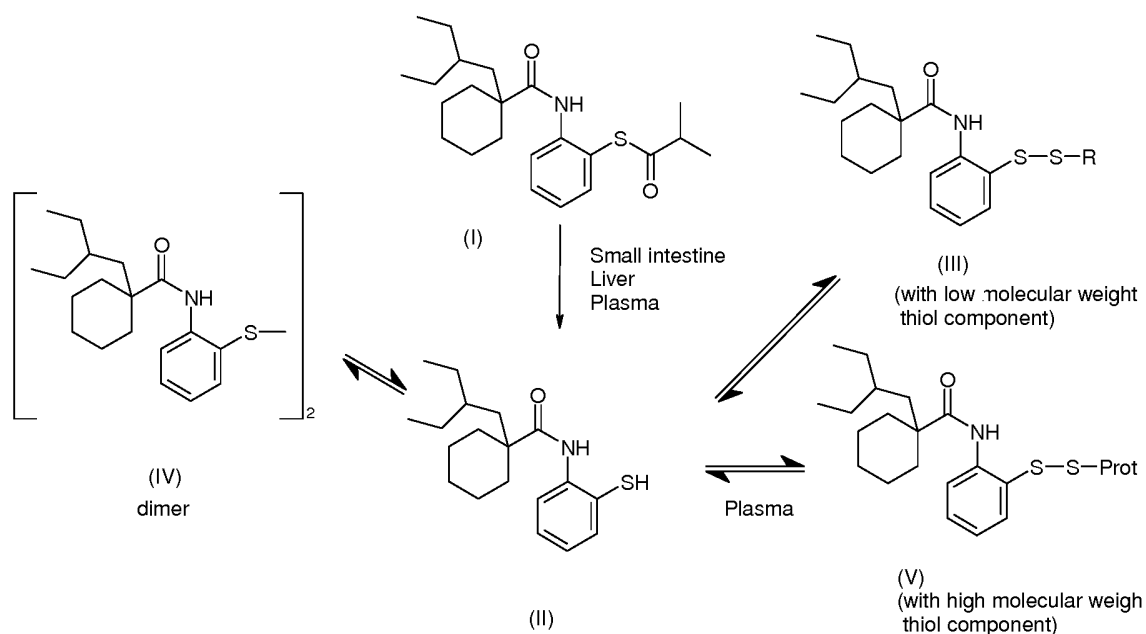
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S-[2-([1-(2-ethylbutyl)-cyclohexyl]-carbonyl)amino)phenyl]2-methylpropanethioate is in crystalline form A.

Form A is characterized by an X-ray powder diffraction pattern having peaks at about 7.9°, 8.5°, 11.7°, 12.7°, 17.1°, 18.0°, 18.5°, 20.2°, 22.1°, 24.7° ± 0.2°, particularly by an XRPD peaks
5 observed at an angle of diffraction 2Theta of 7.9°, 11.7°, 17.1°, 18.5° (±0.2°).

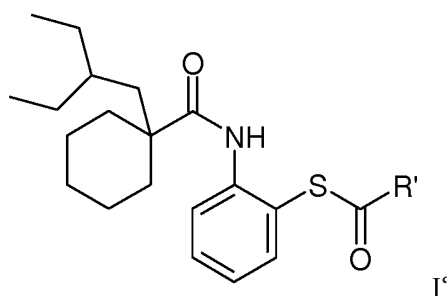
While not wishing to be bound by any particular theory, it is hypothesized that within the body of a patient, Compound I is hydrolyzed in plasma, the liver, and/or the small intestine to form S-[2-([1-(2-ethylbutyl)cyclohexyl]carbonyl)amino)phenyl] thiol (herein referred to as Compound II). It is known that low molecular weight thiol components (i.e., R-SH), such as cysteine and
10 glutathione, and high molecular weight thiol components (i.e., Prot-SH), such as peptides and proteins (e.g., enzymes and cell membranes), exist in the body as mixed disulfides containing an oxidized disulfide bond (S-S bond) between or within the molecule (see, e.g., Shimada et al., J Chromatogr. B, 659, 227 (1994)). Therefore, it is hypothesized that within the body of a
15 patient, Compound II is conjugated with low or high molecular weight thiols to yield mixed disulfides or to yield dimers of Compound II. Since these forms are in an oxidation-reduction equilibrium with each other via Compound II, all of these forms, as well as Compound II, are collectively, but not exclusively, considered and referred to hereafter as the active form of Compound I. The following scheme depicts the above-described hypothesis.

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While the administration of Compound I is a particularly preferred embodiment of the invention, the invention also contemplates the administration of other compounds that will yield the active form of Compound I, i.e., other prodrugs of the active form of Compound I. Such prodrugs, for example, can be compounds that have different mercapto-protecting groups, but that still result in the formation of the active form of Compound I (e.g., Compound II) in the body of a patient (i.e., in vivo). The term "mercapto-protecting groups" refers to commonly used mercapto-protecting groups (e.g., as described in Wolman, *The Chemistry of the Thiol Group*, D. Patai, Ed., Wiley-Interscience, New York, 1974). Any organic residues that can be dissociated in vivo may be used without particular restriction. Examples of particularly suitable mercapto-protecting groups are described in U.S. Patent 6,426,365. The invention further contemplates the administration of Compound I' (wherein R' signifies an organic residue other than an isopropyl group) so as to yield the active form of Compound I.

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In addition, Compounds III, IV, and V (wherein R signifies an organic residue and Prot signifies a peptide or protein), which are believed to be in equilibrium with Compound II in vivo, similarly can be directly administered to the patient.

- 5 The method for assessing the change in conformation of Cholesterol ester transfer protein (CETP), can comprise:

- taking plasma sample from patient treated with a CETP modulator wherein the CETP modulator binds to an epitope within the CETP polypeptide which induces conformational changes;

- 10 - measuring the ability of an antibody to bind or not to the CETP:CETP modulator complex, wherein the antibody binds to an epitope of the CETP polypeptide wherein the said epitope is only accessible (exposed) to the antibody either in the CETP:CETP modulator complex form or in the CETP native form. In Particular the antibody can be JHC 1. JHC-1 antibody can be obtained from Japan Tobacco.
- 15 The antibody can be produced using Balb/c mice immunized against CETP that was partially purified from lipoprotein-depleted healthy human plasma by Phenyl Sepharose HP column (Amersham Pharmacia Biotech) and Resource Q column (Amersham Pharmacia Biotech) chromatographies, in accordance with the disclosure of Takahashi H, Biochem Biophys. Res. Commun 2001, 27, 283, 118.
- 20 Other antibodies were raised in Naval Medical Research Institute (NMRI) mice injected intraperitoneally with 20 µg of rhCETP emulsified in aluminum hydroxide gel (Alhydrogel-2%,

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Brenntag Biosector) containing CPG-OGN according to Davis et al 1998. The animals received four booster injections each at 3-week intervals with the same antigen preparation.

As soon as the animals showed a specific immune response to the recombinant human CETP (rhCETP), the best responders were boosted and after 3 days, the spleens were removed and the
5 isolated cells fused to PAI myeloma cells, a variant of the P3-x63-AG8 myeloma (Köhler & Milstein 1975). The following monoclonal antibodies were selected for further characterization: 6/2, 6/6 6/17.

Although within the hereunder examples 6/6 was used as internal detection antibody/conjugate antibody, it could have easily been replaced by JHC2 from the above mentioned referenced. This
10 antibody would have been produced in similar manner to the procedure disclosed in Takahashi H, Biochem Biophys. Res. Commun 2001, 27, 283, 118.

- More particularly, the method for assessing the change in conformation could be an Enzyme-linked immunosorbent assay (ELISA) method. For instance the ELISA method could be carried out as follows:

- 15 - -apply a solution of plasma sample of a patient being treated with the CETP modulator on the antibodies, in particular JHC1 or 6/2,
- Incubate,
- Rinse the excess,
- Apply a solution of the conjugated antibody, in particular JHC 2 or 6/6,
- 20 - quench the reaction,
- Measure optical density.

Alternatively the method of conformation change can be found in Okamoto H, Nature 2000; 406(6792):203–207.

In a particular embodiment, the invention relates to “CETP modulators” which are useful in the
25 prevention of eye diseases such as cataract, corneal clouding (opacification), glaucoma, uveitis, intraocular neovascular diseases, in particular proliferative retinopathies, choroidal neovascularization (CNV), diabetic and other ischemia-related retinopathies, diabetic macular

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edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization, age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD..

In another particular embodiment, the invention relates “CETP modulators” which are useful in
5 the treatment of eye diseases such as cataract, corneal clouding (opacification), glaucoma, uveitis, intraocular neovascular diseases, in particular proliferative retinopathies, choroidal neovascularization (CNV), diabetic and other ischemia-related retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization, age-
10 related macular degeneration (AMD), more particularly AMD, most particularly dry AMD.

In another particular embodiment, the invention relates “CETP modulators” which are useful in delaying progression of eye diseases such as cataract, corneal clouding (opacification), glaucoma, uveitis, intraocular neovascular diseases, in particular proliferative retinopathies, choroidal neovascularization (CNV), diabetic and other ischemia-related retinopathies, diabetic
15 macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization, age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD.

In another particular embodiment, the invention relates “CETP modulators” which are useful in the reduction of eye diseases such as cataract, corneal clouding (opacification), glaucoma,
20 uveitis, intraocular neovascular diseases, in particular proliferative retinopathies, choroidal neovascularization (CNV), diabetic and other ischemia-related retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization, age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD.

25 In another embodiment, the invention comprises a “CETP modulator” for use as therapeutic active substances for the treatment of eye diseases such as cataract, corneal clouding (opacification), glaucoma, uveitis, intraocular neovascular diseases, in particular proliferative retinopathies, choroidal neovascularization (CNV), diabetic and other ischemia-related

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retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization, age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD.

- 5 In another embodiment, the invention comprises a “CETP modulator” for use as therapeutic active substances for the prophylaxis of eye diseases such as cataract, corneal clouding (opacification), glaucoma, uveitis, intraocular neovascular diseases, in particular proliferative retinopathies, choroidal neovascularization (CNV), diabetic and other ischemia-related retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease,
- 10 histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization, age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD.

- In another embodiment, the invention comprises a “CETP modulator” for use as therapeutic active substances for delaying progression of eye diseases such as cataract, corneal clouding
- 15 (opacification), glaucoma, uveitis, intraocular neovascular diseases, in particular proliferative retinopathies, choroidal neovascularization (CNV), diabetic and other ischemia-related retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization, age-related macular degeneration (AMD), more particularly AMD,
- 20 most particularly dry AMD.

- In another embodiment, the invention comprises a “CETP modulator” for use as therapeutic active substances for the reduction of eye diseases such as cataract, corneal clouding (opacification), glaucoma, uveitis, intraocular neovascular diseases, in particular proliferative retinopathies, choroidal neovascularization (CNV), diabetic and other ischemia-related
- 25 retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization, age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD. In a particular embodiment, the present invention comprises a pharmaceutical composition comprising the cholesteryl ester transfer protein modulator, such as

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5-[2-([1-(2-ethylbutyl)cyclohexyl]carbonyl)amino]phenyl] 2-methylpropanethioate and crosprovidone, useful for the prevention, treatment, delaying progression, and/or reduction of eye diseases, such as cataract, corneal clouding (opacification), glaucoma, uveitis, intraocular neovascular diseases, in particular proliferative retinopathies, choroidal neovascularization (CNV), diabetic and other ischemia-related retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization, age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD.

In another embodiment of the present invention, the composition as described therein is a pharmaceutical composition useful in particular for the prevention of eye diseases such as cataract, corneal clouding (opacification), glaucoma, uveitis, intraocular neovascular diseases, in particular proliferative retinopathies, choroidal neovascularization (CNV), diabetic and other ischemia-related retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization, age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD.

In another embodiment of the present invention, the composition as described therein is a pharmaceutical composition useful in particular for the treatment of eye diseases such as cataract, corneal clouding (opacification), glaucoma, uveitis, intraocular neovascular diseases, in particular proliferative retinopathies, choroidal neovascularization (CNV), diabetic and other ischemia-related retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization, age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD.

In another embodiment of the present invention, the composition as described therein is a pharmaceutical composition useful in particular for delaying progression of eye diseases such as cataract, corneal clouding (opacification), glaucoma, uveitis, intraocular neovascular diseases, in particular proliferative retinopathies, choroidal neovascularization (CNV), diabetic and other ischemia-related retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau

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disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization, age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD.

In another embodiment of the present invention, the composition as described therein is a
5 pharmaceutical composition useful in particular for the reduction of eye diseases such as cataract, corneal clouding (opacification), glaucoma, uveitis, intraocular neovascular diseases, in particular proliferative retinopathies, choroidal neovascularization (CNV), diabetic and other ischemia-related retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal
10 neovascularization, retinal neovascularization, age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD.

In another embodiment, the invention comprises a therapeutic dose of "CETP modulator" for use as therapeutic active substances for the reduction of eye diseases such as cataract, corneal clouding (opacification), glaucoma, uveitis, intraocular neovascular diseases, in particular
15 proliferative retinopathies, choroidal neovascularization (CNV), diabetic and other ischemia-related retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization, age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD. The term "therapeutic dose" in this context means that the
20 compound(s) produce(s) a change in the symptoms or conditions associated with the disease or condition which is being treated. It is sufficient that a therapeutic dose produce an incremental change in the symptoms or conditions associated with the disease; a cure or complete remission of symptoms is not required. One having ordinary skill in this art can easily determine whether a dose is therapeutic by establishing criteria for measuring changes in symptoms or conditions of
25 the disease being treated and then monitoring changes in these criteria according to known methods. External physical conditions, histologic examination of affected tissues in patients or the presence or absence of specific cells or compounds, associated with a disease may provide objective criteria for evaluating therapeutic effect. In one example, methods of the invention may be used to treat AMD where therapeutic effect is assessed by changes in preventing vision loss.
30 Other indicators of therapeutic effect will be readily apparent to one having ordinary skill in the

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art and may be used to establish efficacy of the dose. See also section entitled herein, "Efficacy of the Treatment."

The doses may be administered according to any time schedule which is appropriate for treatment of the disease or condition. For example, the dosages may be administered on a daily, weekly, biweekly or monthly basis in order to achieve the desired therapeutic effect and reduction in adverse effects. The dosages can be administered before, during or after the development of the disorder. The specific time schedule can be readily determined by a physician having ordinary skill in administering the therapeutic compound by routine adjustments of the dosing schedule within the method of the present invention. The time of administration of the number of first individual and second individual doses as well as subsequent dosages is adjusted to minimize adverse effects while maintaining a maximum therapeutic effect. The occurrence of adverse effects can be monitored by routine patient interviews and adjusted to minimize the occurrence of side effects by adjusting the time of the dosing. For example, doses may be administered on a daily schedule.

CETP modulator, which are useful in the prevention, treatment, delaying progression and /or reduction of eye diseases such as cataract, corneal clouding (opacification), glaucoma, uveitis, intraocular neovascular diseases, in particular proliferative retinopathies, choroidal neovascularization (CNV), diabetic and other ischemia-related retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization, age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD, can also be used in association with other active components. For example, compounds of formula (I) can be used in association with anti VEGF compounds.

In the context of the present specification, by "in association with" it should be understood a co-administration, or a combination of two active principles. The coadministration can be simultaneous, almost simultaneous, or delayed in time by a few days or weeks, for example by up to 4 or 5 weeks.

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Vascular endothelial growth factor (VEGF) is an endogenous molecule involved in a number of physiological processes, including blood vessel growth at the foetal stage, during injury healing, or for the growth of new vessels in tissues that have a deficient blood supply. VEGF is also involved in pathological processes, like the development of tumour blood vasculature which
5 allows for growth and spread of the tumour, or the formation of new blood vessels in the eye that eventually contributes to vision loss. AntiVEGF therapies therefore aim to prevent this abnormal blood vessel formation by blocking VEGF action.

Examples of anti-VEGF compounds include Macugen® (Pegaptanib sodium), Lucentis (ranibizumab), Avastatin® (bevacizumab) RhuFab, or VEGF Trap Eye. Therefore, in another
10 aspect, CETP modulator is used in association with antiVEGF compounds for the prevention, treatment and/ or reduction of age-related macular degeneration. In another embodiment, the present invention provides a CETP modulator and one or more carotenoids, in particular wherein the carotenoid are xanthophylls, more particularly wherein the carotenoid are lutein with optionally one stereoisomer of zeaxanthin for the prevention, the treatment, delaying progression
15 and /or the reduction of eye diseases, such as cataract, corneal clouding (opacification), glaucoma, uveitis, intraocular neovascular diseases, in particular proliferative retinopathies, choroidal neovascularization (CNV), diabetic and other ischemia-related retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization,
20 age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD..

In an embodiment, at least one zeaxanthin isomer is selected from the group consisting of zeaxanthin and meso-zeaxanthine. In a further embodiment, the amount of lutein ranges from 0.5 to 25 mg, and the amount of at least one zeaxanthin isomer ranges from 0.1-5 mg.

Advantageously, lutein and at least one zeaxanthin isomer are present in the composition in a
25 ratio lutein:zeaxanthin isomer of about 5: 1. In a preferred embodiment, the association is an intimate mixture of a CETP modulator, lutein and at least one zeaxanthin isomer.

The "CETP modulator" or the composition according to the present invention is for treating mammal (i.e.cat, dog, hamster, rabbit, mouse, gerbil, rat, Guinea pig, or human, especially a human (i. e. a male or female human)).

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Accordingly, the invention provides a method for the treatment or prophylaxis of eye diseases in a mammal, which method comprises administering to a mammal (preferably a mammal in need thereof) a therapeutically effective amount of the pharmaceutical composition. The mammal preferably is a human (i. e. , a male or female human). The human can be of any race (e. g. ,
5 Caucasian or Oriental). The eye diseases is preferably selected from degenerative disease or damage to the retina caused by a disease or an injury, eye strain, accommodative dysfunction of the eye, asthenopia, diabetic retinopathy or dry eye syndrome, the latter caused by either tear or oil gland inflammation. In particular, the method comprises administering a therapeutically effective amount of the composition to an individual to benefit the vision of an individual
10 suffering from eye damage caused by disease or injury or to prevent such disease in man. Most particularly the eye diseases are selected from cataract, corneal clouding (opacification), glaucoma, uveitis, intraocular neovascular diseases, in particular proliferative retinopathies, choroidal neovascularization (CNV), diabetic and other ischemia-related retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye,
15 Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization or age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD.

In certain embodiment of the present invention the composition comprises: 10% to 69% by weight, preferably 40% to 60% by weight, more preferably 48% to 55% by weight of CETP
20 modulator.

In certain embodiments of the present invention, the composition further comprises: 1% to 10% by weight, preferably 5% to 10% by weight, more preferably 4% to 8% by weight of a super-disintegrant.

In certain embodiments of the present invention as defined herein, the super-disintegrant is a
25 hygroscopic polymeric excipient. In particular the hygroscopic polymeric excipient as superdisintegrant is croscarmellose sodium.

In a particular embodiment, the present invention provides a composition comprising:

a) S-[2-([1-(2-ethylbutyl)-cyclohexyl]-carbonyl)amino]phenyl]2-methylpropanethioate,

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b) crospovidone micronized and

c) croscarmellose sodium;

useful for the prevention, treatment, delaying progression, and/or reduction of eye diseases, such as cataract, corneal clouding (opacification), glaucoma, uveitis, intraocular neovascular diseases, in particular proliferative retinopathies, choroidal neovascularization (CNV), diabetic and other ischemia-related retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization or age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD..

- 10 In certain embodiments of the present invention as defined herein, the composition comprises 10% to 69% by weight of S-[2-([1-(2-ethylbutyl)-cyclohexyl]-carbonyl)amino)phenyl]2-methylpropanethioate or a prodrug compound thereof.

In certain embodiments of the present invention, the pharmaceutical composition comprises: 10% to 69% by weight, preferably 40% to 60% by weight, more preferably 48% to 55% by weight of S-[2-([1-(2-ethylbutyl)-cyclohexyl]-carbonyl)amino)phenyl]2-methylpropanethioate or a prodrug compound thereof.

In certain embodiments of the present invention as defined herein, the composition comprises 1% to 10% by weight, preferably 5% to 10% by weight, more preferably 5% to 8% by weight of croscarmellose sodium. More particularly, in a certain embodiment, the composition comprises 5% to 7% by weight of croscarmellose sodium.

In a particular embodiment, the composition comprises:

- 10% to 69% by weight, preferably 40% to 60% by weight, more preferably 48% to 55% by weight of S-[2-([1-(2-ethylbutyl)-cyclohexyl]-carbonyl)amino)phenyl]2-methylpropanethioate;

- 1% to 10% by weight, preferably 5% to 10% by weight, more preferably 4% to 8% by weight of croscarmellose sodium, and

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- 30% to 90% by weight, preferably 34% to 44% by weight, more preferably 40% to 44% by weight of the hygroscopic polymeric excipients;

wherein the hygroscopic polymeric excipients are selected from hydroxypropylmethyl cellulose, microcrystalline cellulose and micronized crosslinked polyvinylpyrrolidone

5 In certain embodiments of the present invention as defined herein, the composition comprises:

a) 48% to 55% by weight of S-[2-([1-(2-ethylbutyl)-cyclohexyl]-carbonyl)amino)phenyl]2-methylpropanethioate;

b) 4% to 8% by weight, of croscarmellose sodium

c) 32% to 41% by weight of water insoluble hygroscopic polymer; and

10 d) 4% to 5% by weight of water soluble hygroscopic polymer.

In certain embodiments of the present invention as defined herein, wherein the hygroscopic polymeric excipients are selected from hydroxypropylmethyl cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, hydroxyethylmethyl cellulose, carboxypolymethylene, methylcellulose, ethylcellulose, hydroxyethyl cellulose, celluloseacetate, polyvinylpyrrolidone, crosslinked polyvinylpyrrolidone, micronized crosslinked polyvinylpyrrolidone, carboxymethylcellulose calcium, crosslinked carboxymethylcellulose, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powder, carboxymethyl starch, starch and pregelatinized starch.

In certain embodiments of the present invention as defined herein, wherein the hygroscopic polymeric excipients are hydroxypropylmethyl cellulose, microcrystalline cellulose and micronized crosslinked polyvinylpyrrolidone.

The pharmaceutical composition can be prepared by any suitable method, such as those methods well known in the art of pharmacy, for example, methods such as those described in Gennaro et al., Remington's Pharmaceutical Sciences (18th ed., Mack Publishing Co., 1990), especially Part 8: Pharmaceutical Preparations and their Manufacture. Such methods include the step of bringing into association the CETP modulator with the other components of the pharmaceutical

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composition. In particular, the composition of the present invention may be prepared according to any known process which results in keeping the API substantially in crystalline form (the amount of the hydrophobic, API in amorphous does not exceed 10% by weight). Furthermore, the composition of the present invention may be prepared according to any known process which results in keeping the API substantially in crystalline form (the amount of the hydrophobic, water instable compound with a waxy consistency substantially in amorphous does not exceed 10% by weight). The composition, in particular the pharmaceutical composition can be prepared according to WO2004/082593 and WO2012/059447.

In certain embodiments of the present invention as defined herein, the two diluents are hygroscopic polymeric excipients. In particular the hygroscopic polymeric excipients as diluents are ethylcellulose, micronized crosslinked polyvinylpyrrolidone, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powder, starch, pregelatinized starch.

In certain embodiments of the present invention as defined herein, at least two hygroscopic polymeric excipients are present.

In certain embodiments of the present invention as defined herein, the super-disintegrant and at least one of the diluents, or at least two diluents are hygroscopic polymeric excipients. More preferably, at least the super-disintegrant and one of the diluents are hygroscopic polymeric excipients.

In certain embodiments of the present invention as defined herein, the super-disintegrant and the two diluents are hygroscopic polymeric excipients.

In certain embodiments of the present invention as defined herein, there is at least 30% by weight of hygroscopic polymeric excipients, preferably 44% to 50% by weight.

In certain embodiments of the present invention, the super-disintegrant is croscarmellose sodium. In particular, the present invention comprises up to 6 % by weight of croscarmellose sodium.

The invention provides a physically stable pharmaceutical composition comprising at least one hydrophobic and water instable cholesteryl ester transfer protein (CETP) modulator or a combination thereof embedded in a chemically protective hygroscopic polymer matrix tablet

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consisting of at least one hygroscopic polymer e.g. hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC), low-substituted hydroxypropyl cellulose (L-HPC), hydroxyethylmethyl cellulose (HEMC), carboxypolymethylene (Carbomer), methylcellulose (MC), ethylcellulose (EC), hydroxyethyl cellulose (HEC), celluloseacetate,
 5 polyvinylpyrrolidone(PVP), crosslinked polyvinylpyrrolidone (Crospovidone), micronized crosslinked polyvinylpyrrolidone (crospovidone micronized), carboxymethylcellulose sodium (croscarmellose sodium, CMC Na), carboxymethylcellulose calcium (croscarmellose calcium, CMC Ca), crosslinked carboxymethylcellulose (Crosslinked CMC), microcrystalline cellulose (MCC), silicified microcrystalline cellulose (silicified MCC), cellulose powder, carboxymethyl
 10 starch (sodium starch glycolate), starch (maize starch, potato starch, rize starch, wheat starch, tapioca starch), pregelatinized starch or a combination thereof in an amount of preferably 40% by weight or more per unit.

According to the present invention the composition comprises at least S-[2-([1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropanethioate or prodrug compound thereof or a
 15 combination thereof embedded in a chemically protective hygroscopic polymer matrix tablet consisting of at least one hygroscopic polymer e.g. hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC), low-substituted hydroxypropyl cellulose (L-HPC), hydroxyethylmethyl cellulose (HEMC), carboxypolymethylene (Carbomer), methylcellulose (MC), ethylcellulose (EC), hydroxyethyl cellulose (HEC), celluloseacetate,
 20 polyvinylpyrrolidone(PVP), crosslinked polyvinylpyrrolidone (Crospovidone), micronized crosslinked polyvinylpyrrolidone (crospovidone micronized), carboxymethylcellulose sodium (croscarmellose sodium, CMC Na), carboxymethylcellulose calcium (croscarmellose calcium, CMC Ca), crosslinked carboxymethylcellulose (Crosslinked CMC), microcrystalline cellulose (MCC), silicified microcrystalline cellulose (silicified MCC), cellulose powder, carboxymethyl
 25 starch (sodium starch glycolate), starch (maize starch, potato starch, rize starch, wheat starch, tapioca starch), pregelatinized starch or a combination thereof in an amount of preferably 40% by weight or more per unit.

In particular according to the present invention the composition comprises at least one hydrophobic and water instable cholesteryl ester transfer protein (CETP) modulator embedded in
 30 a chemically protective hygroscopic polymer matrix tablet consisting of hydroxypropylmethyl

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cellulose, carboxymethylcellulose sodium, microcrystalline cellulose and micronized crosslinked polyvinylpyrrolidone.

In particular according to the present invention the composition comprises at least S-[2-([1-(2-ethylbutyl)-cyclohexyl]-carbonyl)amino)phenyl]2-methylpropanethioate embedded in a chemically protective hygroscopic polymer matrix tablet consisting of hydroxypropylmethyl cellulose, carboxymethylcellulose sodium, microcrystalline cellulose and micronized crosslinked polyvinylpyrrolidone.

In particular embodiment, the composition comprises at least S-[2-([1-(2-ethylbutyl)-cyclohexyl]-carbonyl)amino)phenyl]2-methylpropanethioate embedded in a chemically protective hygroscopic polymer matrix tablet consisting of hydroxypropylmethyl cellulose, carboxymethylcellulose sodium, microcrystalline cellulose and micronized crosslinked polyvinylpyrrolidone in an amount of preferably 40% by weight or more per unit.

In another embodiment of the present invention provides the composition comprises:

- a) 48% to 55% by weight of S-[2-([1-(2-ethylbutyl)-cyclohexyl]-carbonyl)amino)phenyl]2-methylpropanethioate;
- b) less than 12% by weight of crospovidone micronized; and
- c) 35% to 44% by weight of hydroxypropylmethyl cellulose, microcrystalline cellulose and croscarmellose sodium.

In another embodiment of the present invention provides the composition comprises:

- a) S-[2-([1-(2-ethylbutyl)-cyclohexyl]-carbonyl)amino)phenyl]2-methylpropanethioate;
- b) microcrystalline cellulose;
- c) crospovidone micronized;
- d) hydroxypropylmethyl cellulose; and
- e) croscarmellose Sodium.

In another embodiment of the present invention provides the composition comprises:

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- a) 48% to 55% by weight of S-[2-([1-(2-ethylbutyl)-cyclohexyl]-carbonyl)amino)phenyl]2-ethylpropanethioate;
- b) 24% to 26% by weight of microcrystalline cellulose;
- c) 11% to 12% by weight of crospovidone micronized;
- 5 d) 4% to 5% by weight of hydroxypropylmethyl cellulose;
- e) 4% to 6 % by weight of croscarmellose sodium.

In another embodiment of the present invention provides the composition comprises:

- a) 48% to 55% by weight of S-[2-([1-(2-ethylbutyl)-cyclohexyl]-carbonyl)amino)phenyl]2-ethylpropanethioate;
- 10 b) 24% to 26% by weight of microcrystalline cellulose;
- c) 11% to 12% by weight of crospovidone micronized;
- d) 4% to 5% by weight of hydroxypropylmethyl cellulose;
- e) 4% to 6 % by weight of croscarmellose sodium;
- f) 0 to 1% by weight of magnesium stearate;
- 15 g) 0 to 1% by weight of colloidal silicon dioxide;
- h) 0 to 1% by weight of sodium stearyl fumarate.

In particular embodiments of the present invention, the compositions described herein are pharmaceutical compositions.

The pharmaceutical composition can be, for example, in the form of a pill, capsule or tablet, each
20 containing a predetermined amount of CETP modulator and in particular coated for ease of swallowing, in the form of a powder or granules. In particular, the pharmaceutical composition is in the form of a tablet comprising the CETP modulator and the components of the tablet utilized and described therein. For oral administration, fine powders or granules may contain diluting, dispersing and/or surface active agents and may be present, for example, in capsules or sachets in
25 the dry state, or in tablets wherein binders and lubricants may be included. Components such as sweeteners, flavoring agents, preservatives, suspending agents, thickening agents, and/or emulsifying agents also may be present in the pharmaceutical composition.

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In a particular embodiment, the composition herein is filmed coated, with polyvinyl alcohol based coat (PVA-based coat), particularly with 20 mg or less PVA-based coat, more particularly with 15 mg PVA-based coat.

In certain embodiments of the present invention, the composition comprises 100 mg to 600 mg of S-[2-([1-(2-ethylbutyl)-cyclohexyl]-carbonyl)amino)phenyl]2-methylpropanethioate. In particular, the composition comprises 150 mg to 450 mg of S-[2-([1-(2-ethylbutyl)-cyclohexyl]-carbonyl)amino)phenyl]2-methylpropanethioate. More particularly, the composition comprises 250 mg to 350 mg of S-[2-([1-(2-ethylbutyl)-cyclohexyl]-carbonyl)amino)phenyl]2-methylpropanethioate. Most particularly, the composition comprises 250 mg to 350 mg of S-[2-([1-(2-ethylbutyl)-cyclohexyl]-carbonyl)amino)phenyl]2-methylpropanethioate.

In another embodiment, the composition comprises for pediatric use 25mg to 300mg of S-[2-([1-(2-ethylbutyl)-cyclohexyl]-carbonyl)amino)phenyl]2-methylpropanethioate. In particular the pediatric composition comprises 75mg to 150mg of S-[2-([1-(2-ethylbutyl)-cyclohexyl]-carbonyl)amino)phenyl]2-methylpropanethioate.

To be effective, CETP modulator must be absorbed into the blood. Oral dosing of CETP modulator is preferred because to be effective such "CETP modulators" must be taken on a regular basis, such as daily.

The CETP modulator can be administered to the mammal at any suitable dosage (e. g. , to achieve a therapeutically effective amount). For example, a suitable dose of a therapeutically effective amount of compound of formula I for administration to a patient will be between approximately 100 mg to about 1800 mg per day. In particular, a desirable dose is about 300 mg to about 900 mg per day. A preferred dose is about 600 mg per day.

In another embodiment the invention provides a kit comprising a CETP modulator as described herein, lutein and optionally with one or more stereoisomer of zeaxanthin. In a more particular embodiment the invention provides a kit comprising a CETP modulator as described herein, lutein and optionally with one or more stereoisomer of zeaxanthin., prescribing information also known as "leaflet", a blister package or bottle (HDPE or glass) and a container. The prescribing information preferably includes the advice to a patient regarding the administration of the CETP

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modulator (e.g. compound of formula (I) with food, especially to improve the bioavailability of the CETP modulator.

In another embodiment the invention provides a kit comprising a composition as described herein, lutein and optionally with one or more stereoisomer of zeaxanthin. In a more particular
5 embodiment the invention provides a kit comprising a composition as described herein, lutein and optionally with one or more stereoisomer of zeaxanthin, prescribing information also known as "leaflet", a blister package or bottle (HDPE or glass) and a container. The prescribing information preferably includes the advice to a patient regarding the administration of the CETP modulator (e.g. compound of formula (I) with food, especially to improve the bioavailability of
10 the CETP modulator.

In another embodiment, the invention provides a kit comprising a composition comprising a therapeutically effective amount of S-[2-([1-(2-ethylbutyl)-cyclohexyl]-carbonyl)amino)phenyl]2-methylpropanethioate and at least 30% by weight of hygroscopic polymeric excipients by composition weight, lutein and optionally with one or more
15 stereoisomer of zeaxanthin., prescribing information, a blister package or bottle and a container. In particular embodiment the invention provides the kit as described herein, wherein the prescribing information includes the advice to a patient regarding the administration of S-[2-([1-(2-ethylbutyl)-cyclohexyl]-carbonyl)amino)phenyl]2-methylpropanethioate with food.

In another embodiment, the invention provides a tablet comprising the composition as herein
20 described.

In another embodiment, the invention provides a composition as herein described for preparing a medicament for the treatment or prevention of eye diseases, such as cataract, corneal clouding (opacification), glaucoma, uveitis, intraocular neovascular diseases, in particular proliferative retinopathies, choroidal neovascularization (CNV), diabetic and other ischemia-related
25 retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization or age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD, in particular wherein the S-[2-([1-(2-ethylbutyl)-cyclohexyl]-

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carbonyl]amino)phenyl]2-methylpropanethioate is administered at a daily dose of 100mg to 1800mg, particularly 300mg to 900mg, more particularly 600mg, more particularly wherein S-[2-([[1-(2-ethylbutyl)-cyclohexyl]-carbonyl]amino)phenyl]2-methylpropane thioate is administered with food.

- 5 Other features and embodiments of the invention will become apparent from the following examples which are given for illustration of the invention rather than for limiting its intended scope.

Example A:

XRPD patterns of S-[2-([1-(2-ethylbutyl)cyclohexyl] carbonyl] amino) phenyl] 2-methylpropanethioate crystalline form A were recorded at ambient conditions in transmission geometry with a STOE STADI P diffractometer (Cu K alpha radiation source, primary monochromator, position sensitive detector, angular range 3° to 42° 2Theta, approximately 60 minutes total measurement time). The samples were prepared and analyzed without further processing (e.g. grinding or sieving) of the substance.

2theta / °	relative intensity / %
7.9	86.3
8.5	16.2
11.7	30.7
12.7	17.1
17.1	41.6

2theta / °	relative intensity / %
18	14.6
18.5	100
20.2	27.2
22.1	33.7
24.7	11.9

10 Example 1: Golden Syrian hamsters study a:

MATERIAL AND METHODS

Hamsters (7 weeks-old) were fed a standard rodent chow diet containing 4.5% fat and 0.05% cholesterol and coconut oil (70 g/kg dry food) for 14 days. After two weeks of feeding, hamsters were allocated to 2 experimental groups of 10 animals and given the same diet as before supplemented with 0.1% (w:w) FLORAGLO (lutein 5.2 %, zeaxanthin 0.5%, DSM Nutritional Products): group 1 received no treatment, group 2 was given dalcetrapib as a 0.375% food admixture (~400 mg/kg).

After 14 days of treatment and 4 hours of fasting, plasma, liver and eyes were collected and kept frozen until analysis. Lutein and zeaxanthin levels in plasma, liver and the

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pooled eyecups from 2 hamsters were determined by HPLC-MS using cryptoxanthin as internal standard. Plasma samples were directly extracted with hexane/ethyl acetate in dark environment in the presence of BHT. Liver samples and pooled eye cups (n=4) were first homogenized in the presence of BHT using an appropriate solvent in a Precellys tissue homogenizer followed by saponification prior extraction with hexane/ethyl acetate. The organic phase was washed with water. All organic phases were dried and reconstituted in methanol containing 0.1%. HPLC-MS was accomplished on a Waters TQ-S in APCI mode coupled to an Acquity I-class UPLC (Waters AG, Baden-Dättwil) on an ACCLAIM C30 RP column (Thermo Fisher Scientific, Reinach).

10 Results

Change in plasma, liver and eyecups following dalcetrapib treatment.

	Lutein	Zeaxanthin
Plasma	+ 55.7	+ 164
<i>p</i>	**	***
Liver	+ 107	+ 222.9
<i>p</i>	***	***
Eyecups	+ 164.6	+ 114
<i>p</i>	***	***

In % vs control; Wilcoxon / Kruskal-Wallis's test

* $p < 0.05$; ** : $p < 0.01$; *** : $p < 0.001$

Dalcetrapib increased significantly plasma, liver and eyecup lutein levels by +55.7% $p < 0.0019$, +107% $p < 0.0002$ and +165% $p < 0.0002$ and zeaxanthin levels by +164% $p < 0.0002$, +222.9% $p < 0.0002$ and +114 % $p < 0.0088$.

Example 2: Golden Syrian hamsters study b:

MATERIAL AND METHODS

Hamsters (7 weeks-old) were fed a standard rodent chow diet containing 4.5% fat and 0.05% cholesterol and coconut oil (70 g/kg dry food) for 14 days. After 2 weeks of high-fat diet feeding, hamsters were allocated to 3 experimental treatment groups of 10 animals each based on plasma lipid levels, and provided the same diet as before supplemented with 0.1% (w/w) FLORAGLO (same composition as for Study 2) and either no treatment

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(group 1), dalcetrapib at 0.320% (w:w, ~300 mg/kg, group 2), or anacetrapib at 0.024% (w:w, ~25 mg/kg, group 3).

After 14 days of treatment, plasma and livers were collected for lutein and zeaxanthin analysis as described in study a.

5

Results

Change in plasma and liver following dalcetrapib and anacetrapib treatment.

	dalcetrapib		anacetrapib	
	Lutein	zeaxanthin	Lutein	zeaxanthin
Plasma	+ 95	+ 101	ns	ns
<i>p</i>	***	***		
Liver	+ 90	+ 109	-32	-31
<i>p</i>	**	***	*	*

In % vs control; Wilcoxon / Kruskal-Wallis's test

* $p < 0.05$; ** : $p < 0.01$; *** : $p < 0.001$

10 It can be concluded from both in vivo studies that dalcetrapib treatment increases the intestinal uptake and tissue distribution of the protective antioxidant dietary xanthophylls such as lutein and zeaxanthin.

Additional variable measured.

	Dalcetrapib	Anacetrapib
Total cholesterol	ns	+28 **
HDL-C	ns	+54 ***
VLDL-C	-27 *	ns
LDL-C	ns	-99 ***
Triglycerides	-37 **	ns

In % vs control; Wilcoxon / Kruskal-Wallis's test

15 * : $p < 0.05$; ** : $p < 0.01$; *** : $p < 0.001$

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CLAIMS

1. A CETP modulator for use in the prevention, treatment, delaying progression and /or reduction of eye disease. .
2. A CETP modulator according to claim 1 for use in the treatment of eye disease.
- 5 3. A CETP modulator according to any one of claim 1 or 2, wherein the eye disease is cataract, corneal clouding (opacification), glaucoma, uveitis or intraocular neovascular diseases.
4. A CETP modulator according to any one of claims 1 to 3, wherein the eye disease is proliferative retinopathies, Choroidal Neovascularization (CNV), diabetic and other
10 ischemia-related retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization or age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD
5. A CETP modulator according to any one of claims 1 to 4 in association with an
15 anti-VEGF compound.
6. A CETP modulator according to any one of claims 1 to 5 wherein the anti-VEGF compound is Macugen, Lucentis or Avastatin.
7. A CETP modulator according to any one of claims 1 to 6, in association with one or more carotenoids.
- 20 8. A CETP modulator according to any one of claims 1 to 7, wherein the carotenoids are xanthophylls.
9. A CETP modulator according to any one of claims 1 to 8, in association with lutein or with one stereoisomer of zeaxanthin or a mixture thereof.
10. A CETP modulator according to any one of claims 1 to 9, in association with lutein
25 optionally with one stereoisomer of zeaxanthin.

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11. A CETP modulator according to any one of claims 1 to 10 wherein the CETP modulator is 5-[2-([1-(2-ethylbutyl)cyclohexyl]carbonyl)amino)phenyl] 2-methylpropanethioate.
12. A CETP modulator according to any one of claims 1 to 11, wherein the CETP
5 modulator is a prodrug that forms S-[2-([1-(2-ethylbutyl)cyclohexyl]carbonyl)amino)phenyl] thiol *in vivo*
13. A method of preventing, retarding and ameliorating eye disease which comprises administering a CETP modulator.
14. A method for treating eye disease according to claim 13 which comprises
10 administering a CETP modulator.
15. A method according to any one of claims 13 to 14, wherein the eye disease is cataract, corneal clouding (opacification), glaucoma, uveitis or intraocular neovascular diseases.
16. A method according to any one of claims 13 to 14, wherein the eye disease is
15 proliferative retinopathies, Choroidal Neovascularization (CNV), diabetic and other ischemia-related retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization or age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD.
- 20 17. A method according to any one of claims 13 to 16, which further comprises administering an anti-VEGF compound.
18. A method according to any one of claims 13 to 17 wherein the anti-VEGF compound is Macugen, Lucentis or Avastatin.
19. A method according to any one of claims 13 to 18, which further comprises
25 administering one or more carotenoids, in particular with one or more xanthophylls, more particularly with lutein optionally with one stereoisomer of zeaxanthin.

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20. A method according to any one of claims 13 to 19, wherein the CETP modulator is 5-[2-([1-(2-ethylbutyl)cyclohexyl]carbonyl)amino)phenyl] 2-methylpropanethioate.
21. A method according to any one of claims 13 to 20, wherein the CETP modulator is a prodrug that forms S-[2-([1-(2-ethylbutyl)cyclohexyl]carbonyl)amino)phenyl] thiol
5 *in vivo*.
22. A pharmaceutical composition comprising 5-[2-([1-(2-ethylbutyl)cyclohexyl]carbonyl)amino)phenyl] 2-methylpropanethioate or the prodrug compound thereof and crospovidone, useful for the prevention, treatment, delaying progression, and/or reduction of eye diseases.
- 10 23. A pharmaceutical composition according to claim 22, which further comprises one or more carotenoids.
24. A pharmaceutical composition according to any one of claims 22 to 23, wherein the carotenoids are xanthophylls.
25. A pharmaceutical composition according to claim 21, which further comprises
15 lutein or with one stereoisomer of zeaxanthin or a mixture thereof.
26. A pharmaceutical composition according to any one of claims 22 to 25, which further comprises an anti-VEGF compound.
27. A pharmaceutical composition according to any one of claims 22 to 26, wherein the anti-VEGF compound is Macugen, Lucentis or Avastatin.
- 20 28. A pharmaceutical composition according to any one of claims 22 to 27, wherein the eye disease is proliferative retinopathies, Choroidal Neovascularization (CNV), diabetic and other ischemia-related retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal
25 neovascularization or age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD.

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29. A kit comprising a CETP modulator according to any one of claims 1 to 7, lutein and optionally with one or more stereoisomer of zeaxanthin.
30. A kit according to claim 29, which further comprises prescribing information also known as “leaflet”, a blister package or bottle (HDPE or glass) and a container.
- 5 31. A kit according to any one of claims 29 to 30 wherein the eyes disease is proliferative retinopathies, Choroidal Neovascularization (CNV), diabetic and other ischemia-related retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO),
10 corneal neovascularization, retinal neovascularization or age-related macular degeneration (AMD), more particularly AMD, most particularly dry AMD..
32. A kit according to any one of claims 29 to 30 wherein the eyes disease is age-related macular degeneration.
33. The invention as hereinbefore described.

Figure 1

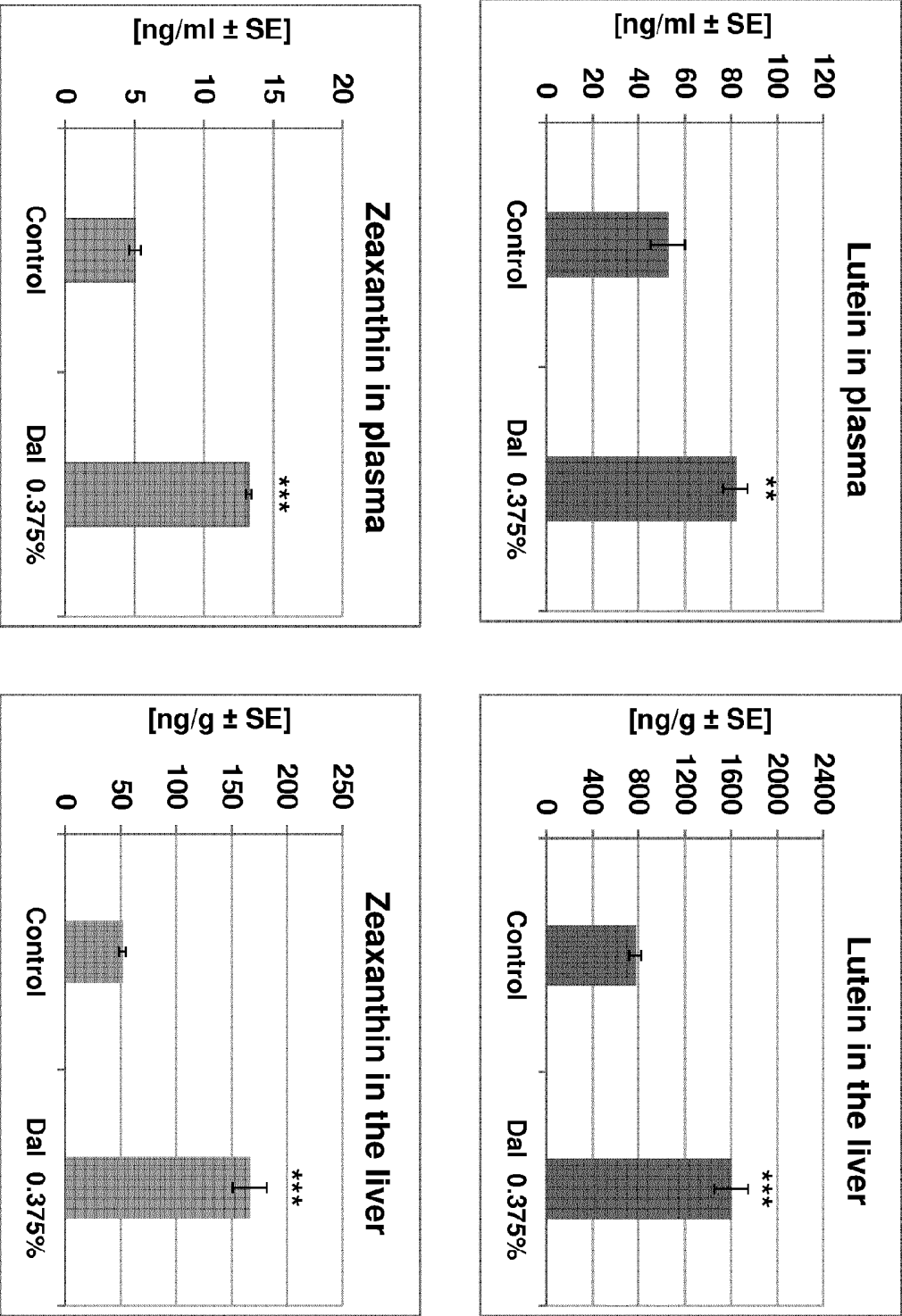


Figure 2

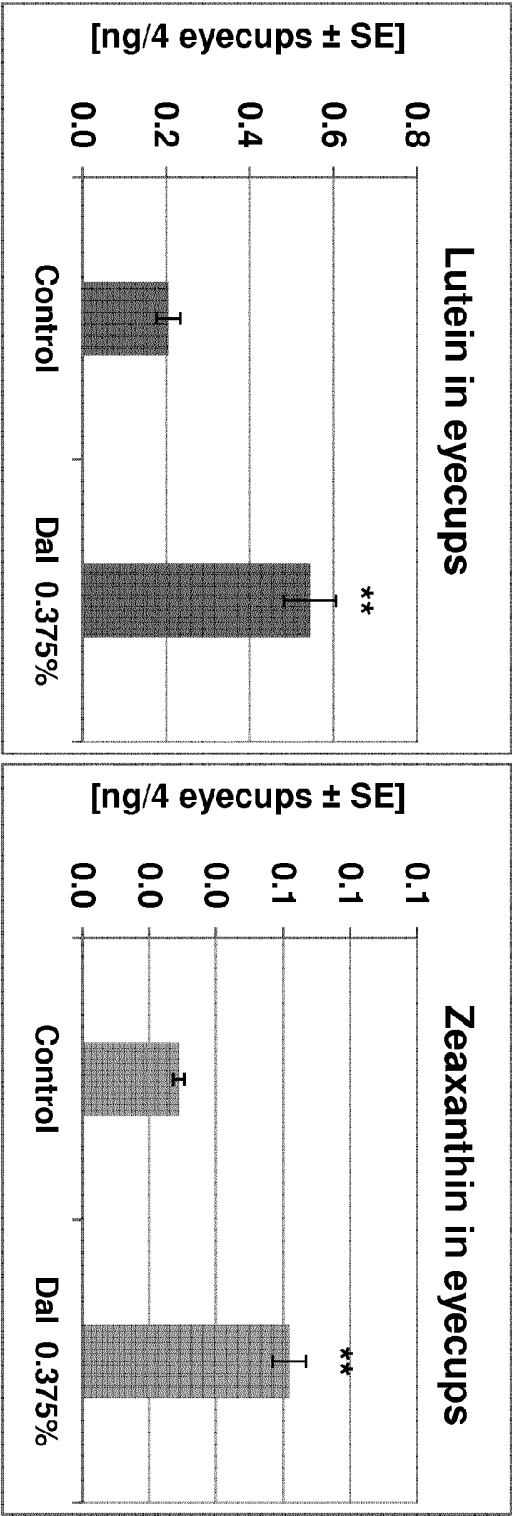
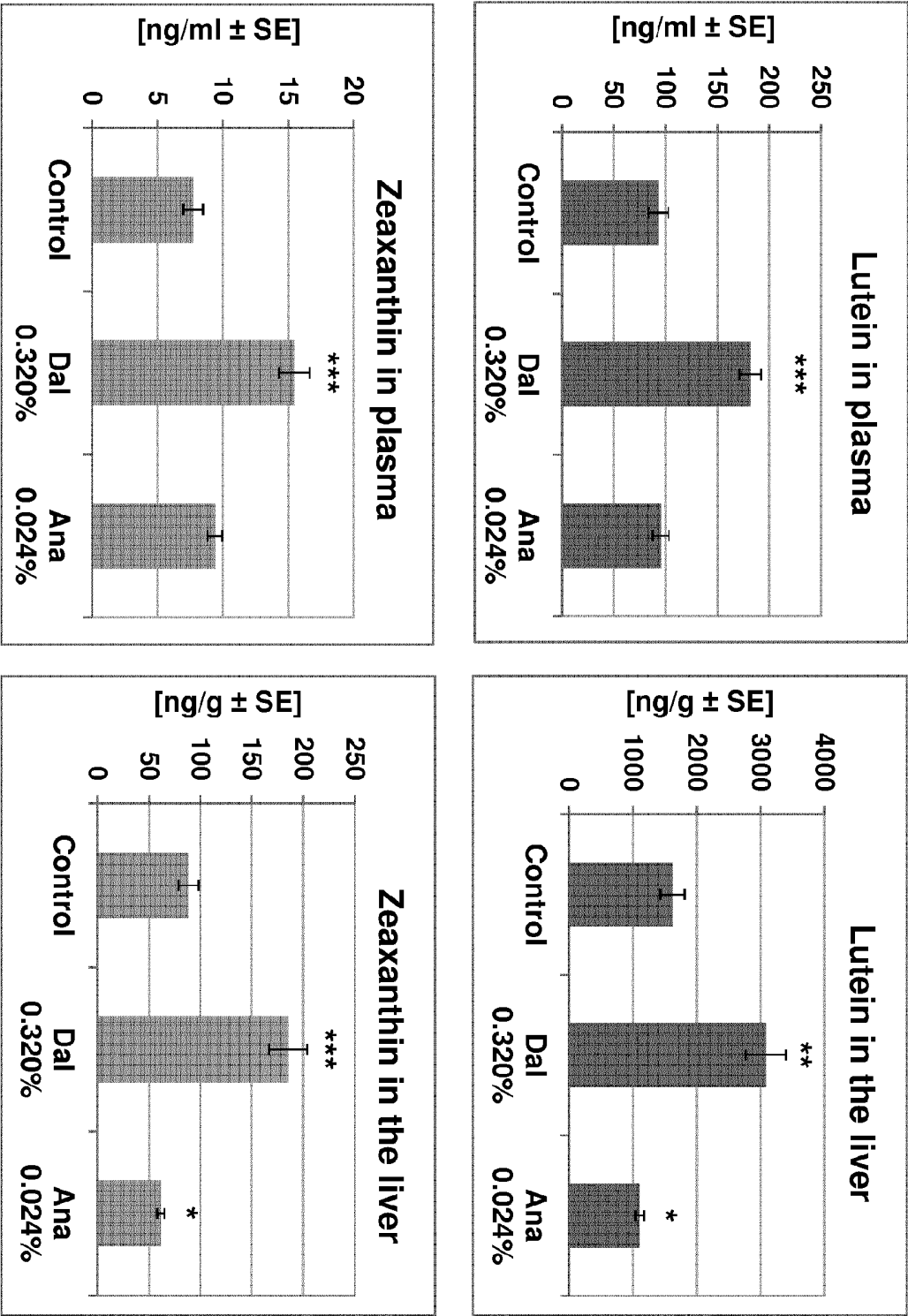


Figure 3



INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2014/077855

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 12, 21, 33(completely); 22(partially)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/077855

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/167 A61P27/02
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

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)

EP0-Internal, BIOSIS, WPI Data, CHEM ABS Data, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Kristin J Meyers ET AL: "Genetic Evidence for Role of Carotenoids in Age-Related Macular Degeneration in the Carotenoids in Age-Related Eye Disease Study (CAREDS)", Invest Ophthalmol Vis Sci, 17 December 2013 (2013-12-17), pages 587-599, XP055156730, Retrieved from the Internet: URL:http://www.iovs.org/content/55/1/587.full.pdf [retrieved on 2014-12-04] page 594, left hand column, 2nd full paragraph; table 1 ----- -/--	1-11, 13-20, 22-32



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search

10 February 2015

Date of mailing of the international search report

19/02/2015

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Borst, Markus

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2014/077855

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	I. NAKATA ET AL: "Association Between the Cholesteryl Ester Transfer Protein Gene and Polypoidal Choroidal Vasculopathy", INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE, vol. 54, no. 9, 9 September 2013 (2013-09-09), pages 6068-6073, XP055156770, ISSN: 0146-0404, DOI: 10.1167/iovs.13-11605 abstract; table 2	1-11, 13-20, 22-32
A	PATRICK BOREL ET AL: "Human fasting plasma concentrations of vitamin E and carotenoids, and their association with genetic variants in apo C-III, cholesteryl ester transfer protein, hepatic lipase, intestinal fatty acid binding protein and microsomal triacylglycerol transfer protein", BRITISH JOURNAL OF NUTRITION, vol. 101, no. 05, 29 July 2008 (2008-07-29), page 680, XP055156833, ISSN: 0007-1145, DOI: 10.1017/S0007114508030754 abstract; table 3	1-11, 13-20, 22-32
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X	US 2012/301439 A1 (APTE RAJENDRA S [US]) 29 November 2012 (2012-11-29)	1-4,11, 13-16,20
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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2014/077855

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	ERIC J. NIESOR ET AL: "Effect of Compounds Affecting ABCA1 Expression and CETP Activity on the HDL Pathway Involved in Intestinal Absorption of Lutein and Zeaxanthin", LIPIDS, vol. 49, no. 12, 10 October 2014 (2014-10-10), pages 1233-1243, XP055156717, ISSN: 0024-4201, DOI: 10.1007/s11745-014-3958-8 abstract -----	1-11, 13-20, 22-32

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 12, 21, 33(completely); 22(partially)

Claims 12, 21 and part of claim 22 are directed to "a prodrug that forms dalcetrapib" . The application, however, does not provide any teaching as to which compounds are metabolised into dalcetrapib or how to identify such compounds. Consequently, the subject-matter of these (parts of) claims cannot be subject to search nor to examination.

Claim 33 is drafted as "omnibus claim" without clearly defining the subject-matter for which protection is sought. Consequently, the subject-matter of this claim cannot be subject to search nor to examination.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2014/077855

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(71)申请人 豪夫迈·罗氏有限公司

地址 瑞士巴塞尔

(72)发明人 埃弗利娜·沙皮

埃里克·J·尼泽尔

(74)专利代理机构 中科专利商标代理有限责任
公司 11021

代理人 贺卫国 柳春琦

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权利要求书2页 说明书22页 附图3页

(54)发明名称

用于治疗眼疾病的CETP调节剂

(57)摘要

本发明涉及CETP调节剂,其可用于预防、治疗眼疾病、延迟眼疾病的进展和/或减少眼疾病。

1. 一种CETP调节剂,其用于预防、治疗眼疾病、延迟眼疾病的进展和/或减少眼疾病。
2. 根据权利要求1所述的CETP调节剂,其用于治疗眼疾病。
3. 根据权利要求1或2中任一项所述的CETP调节剂,其中所述眼疾病是白内障、角膜混浊(浑浊化)、青光眼、葡萄膜炎或眼内新生血管性疾病。
4. 根据权利要求1至3中任一项所述的CETP调节剂,其中所述眼疾病是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞(CRVO)、角膜新生血管形成、视网膜新生血管形成或年龄相关性黄斑变性(AMD),更特别是AMD,最特别是干性AMD。
5. 根据权利要求1至4中任一项所述的CETP调节剂,其与抗-VEGF化合物联合。
6. 根据权利要求1至5中任一项所述的CETP调节剂,其中所述抗-VEGF化合物是哌加他尼钠、雷珠单抗或阿瓦斯丁。
7. 根据权利要求1至6中任一项所述的CETP调节剂,其与一种或多种类胡萝卜素联合。
8. 根据权利要求1至7中任一项所述的CETP调节剂,其中所述类胡萝卜素是叶黄素。
9. 根据权利要求1至8中任一项所述的CETP调节剂,其与黄体素或与玉米黄质的一种立体异构体或其混合物联合。
10. 根据权利要求1至9中任一项所述的CETP调节剂,其与任选地与玉米黄质一种立体异构体一起的黄体素联合。
11. 根据权利要求1至10中任一项所述的CETP调节剂,其中所述CETP调节剂是5-[2-([1-(2-乙基丁基)环己基]羰基)氨基)苯基]2-甲基硫代丙酸酯。
12. 根据权利要求1至11中任一项所述的CETP调节剂,其中所述CETP调节剂是在体内形成S-[2-([1-(2-乙基丁基)环己基]羰基)氨基)苯基]硫醇的前药。
13. 一种预防、减缓和改善眼疾病的方法,其包括施用CETP调节剂。
14. 根据权利要求13所述的用于治疗眼疾病的方法,其包括施用CETP调节剂。
15. 根据权利要求13至14中任一项所述的方法,其中所述眼疾病是白内障、角膜混浊(浑浊化)、青光眼、葡萄膜炎或眼内新生血管性疾病。
16. 根据权利要求13至14中任一项所述的方法,其中所述眼疾病是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞(CRVO)、角膜新生血管形成、视网膜新生血管形成或年龄相关性黄斑变性(AMD),更特别是AMD,最特别是干性AMD。
17. 根据权利要求13至16中任一项所述的方法,其还包括施用抗-VEGF化合物。
18. 根据权利要求13至17中任一项所述的方法,其中所述抗-VEGF化合物是哌加他尼钠、雷珠单抗或阿瓦斯丁。
19. 根据权利要求13至18中任一项所述的方法,其还包括施用一种或多种类胡萝卜素,尤其是与一种或多类叶黄素一起,更特别是与任选地与玉米黄质的一种立体异构体一起的黄体素一起。
20. 根据权利要求13至19中任一项所述的方法,其中所述CETP调节剂是5-[2-([1-(2-乙基丁基)环己基]羰基)氨基)苯基]2-甲基硫代丙酸酯。

21. 根据权利要求13至20中任一项所述的方法, 其中所述CETP调节剂是在体内形成S-[2-([1-(2-乙基丁基)环己基]羰基]氨基)苯基]硫醇的前药。

22. 一种药物组合物, 其包含5-[2-([1-(2-乙基丁基)环己基]羰基]氨基)苯基]2-甲基硫代丙酸酯或其前药化合物和交聚维酮, 可用于预防、治疗眼疾病、延迟眼疾病的进展和/或减少眼疾病。

23. 根据权利要求22所述的药物组合物, 其还包含一种或多种类胡萝卜素。

24. 根据权利要求22至23中任一项所述的药物组合物, 其中所述类胡萝卜素是叶黄素。

25. 根据权利要求21所述的药物组合物, 其还包含黄体素或与玉米黄质的一种立体异构体或其混合物一起。

26. 根据权利要求22至25中任一项所述的药物组合物, 其还包含抗-VEGF化合物。

27. 根据权利要求22至26中任一项所述的药物组合物, 其中所述抗-VEGF化合物是哌加他尼钠、雷珠单抗或阿瓦斯丁。

28. 根据权利要求22至27中任一项所述的药物组合物, 其中所述眼疾病是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞(CRVO)、角膜新生血管形成、视网膜新生血管形成或年龄相关性黄斑变性(AMD), 更特别是AMD, 最特别是干性AMD。

29. 一种试剂盒, 其包含根据权利要求1至7中任一项所述的CETP调节剂, 黄体素并且任选地与玉米黄质的一种或多种立体异构体一起。

30. 根据权利要求29所述的试剂盒, 其还包括处方信息, 也称为“说明书”, 泡罩包装或瓶(HDPE或玻璃)和容器。

31. 根据权利要求29至30中任一项所述的试剂盒, 其中所述眼疾病是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞(CRVO)、角膜新生血管形成、视网膜新生血管形成或年龄相关性黄斑变性(AMD), 更特别是AMD, 最特别是干性AMD。

32. 根据权利要求29至30中任一项所述的试剂盒, 其中所述眼疾病是年龄相关性黄斑变性。

33. 如上文所述的发明。

用于治疗眼疾病的CETP调节剂

[0001] 本发明涉及CETP调节剂,其可用于预防、治疗眼疾病、延迟眼疾病的进展和/或减少眼疾病,所述眼疾病如白内障(cataract)、角膜混浊(corneal clouding)(浑浊化(opacification))、青光眼(glaucoma)、葡萄膜炎(uveitis)、眼内新生血管性疾病,尤其是增生性视网膜病变(proliferative retinopathies)、脉络膜新生血管形成(Choroidal Neovascularization,CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿(diabetic macular edema)、病理性近视(pathological myopia)、脑视网膜血管瘤病(von Hippel-Lindau disease)、眼组织胞浆菌病(histoplasmosis of the eye)、视网膜中央静脉阻塞(Central Retinal Vein Occlusion,CRVO)、角膜新生血管形成(corneal neovascularization)、视网膜新生血管形成(retinal neovascularization)、年龄相关性黄斑变性(age-related macular degeneration,AMD),更特别是AMD,最特别是干性AMD,以及其预防、减缓和改善眼疾病的方法,所述眼疾病如白内障、角膜混浊(浑浊化)、青光眼、葡萄膜炎、眼内新生血管性疾病,尤其是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞(CRVO)、角膜新生血管形成、视网膜新生血管形成、年龄相关性黄斑变性(AMD),更特别是AMD,最特别是干性AMD。

[0002] 在另一实施方案中,本发明包括CETP调节剂,其用作治疗活性物质,用于预防(prevention)、治疗、预防(prophylaxis)和/或减少眼疾病,如白内障、角膜混浊(浑浊化)、青光眼、葡萄膜炎、眼内新生血管性疾病,尤其是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞(CRVO)、角膜新生血管形成、视网膜新生血管形成、年龄相关性黄斑变性(AMD),更特别是AMD,最特别是干性AMD。

[0003] 在特定实施方案中,本发明包括药物组合物,所述药物组合物包含CETP调节剂,尤其是5-[2-([1-(2-乙基丁基)环己基]羰基)氨基)苯基]2-甲基硫代丙酸酯,和交聚维酮(尤其是微粒化的交聚维酮),其可用于预防、治疗眼疾病、延迟眼疾病进展和/或减少眼疾病,如白内障、角膜混浊(浑浊化)、青光眼、葡萄膜炎、眼内新生血管性疾病,尤其是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞(CRVO)、角膜新生血管形成、视网膜新生血管形成、年龄相关性黄斑变性(AMD),更特别是AMD,最特别是干性AMD。

[0004] 在本发明的另一实施方案中,涉及组合物,所述组合物包括CETP调节剂,其与一种或多种类胡萝卜素联合,尤其是其中所述类胡萝卜素选自叶黄素,更特别是其中一种类胡萝卜素是黄体素,最特别是其中类胡萝卜素是黄体素和玉米黄质的一种立体异构体(更特别是玉米黄质),可用于预防、治疗眼疾病,延迟眼疾病的进展,和/或减少眼疾病,所述眼疾病如白内障、角膜混浊(浑浊化)、青光眼、葡萄膜炎、眼内新生血管性疾病,尤其是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞(CRVO)、角膜新生

血管形成、视网膜新生血管形成、年龄相关性黄斑变性(AMD),更特别是AMD,最特别是干性AMD。所述组合物是营养组合物或药物组合物,其尤其是可用于预防、治疗眼疾病、延迟眼疾病进展、和/或减少眼疾病,所述眼疾病如白内障、角膜混浊(浑浊化)、青光眼、葡萄膜炎、眼内新生血管性疾病,尤其是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞(CRVO)、角膜新生血管形成、视网膜新生血管形成、年龄相关性黄斑变性(AMD),更特别是AMD,最特别是干性AMD。

[0005] 在根据本发明的特定实施方案中,所述眼疾病是白内障、角膜混浊(浑浊化)、年龄相关性黄斑变性(AMD),尤其是AMD。

[0006] 附图简述:

[0007] 图1:喂食FLORAGLO的仓鼠研究a中达塞曲匹(Dalcetrapib,Dal)对血浆和肝黄体素和玉米黄质水平的影响。

[0008] 图2:喂食FLORAGLO的仓鼠研究a中达塞曲匹(Dal)对视杯(eyecups)黄体素和玉米黄质水平的影响。

[0009] 图3:喂食FLORAGLO的仓鼠研究b中达塞曲匹(Dal)和安塞曲匹(Anacetrapib,Ana)对血浆和肝黄体素和玉米黄质水平的影响。

[0010] 类胡萝卜素是天然存在的具有抗氧化性质的化合物。类胡萝卜素是由植物合成的常见化合物,并且大大促进植物和一些动物的着色。大部分的动物物种(包括哺乳动物)不能重新合成类胡萝卜素并且因此依赖膳食提供类胡萝卜素需求。哺乳动物还具有有限的修饰类胡萝卜素的能力。哺乳动物可以将 β -胡萝卜素转化为维生素A,但大多数其他类胡萝卜素以未改变的形式存放在哺乳动物组织中。就人来说,在血清中发现大约十种类胡萝卜素。血清中的主要的类胡萝卜素是 β -胡萝卜素, α -胡萝卜素,隐黄素,番茄红素和黄体素。在人器官中发现少量的玉米黄质,六氢番茄红素,和八氢番茄红素。

[0011] 血浆番茄红素、黄体素和 β -胡萝卜素是用于说明人血清中氧化修饰的LDL的浓度的最有力的抗氧化剂(Karppi J等人Atherosclerosis 2010April;209(2):565)。在观察的社会动脉粥样硬化风险(Atherosclerosis Risk in Communities,ARIC)中的参与者中,研究群体患者基于B-模式颈动脉超声图选择,是231个无症状的年龄-、性别-、种族-、和领域中心-匹配的病例对照对。在对可能的混杂因素进行调节后,仅黄体素加上玉米黄质与无症状动脉粥样硬化的反向关联被保持。该研究支持在一些类胡萝卜素(特别是黄体素加上玉米黄质)的循环水平和颈动脉内膜中层厚度(IMT)之间适度的反向关联(Iribarren C等人Arterioscler Thromb Vasc Biol 1997年6月;17(6):1171)。Dwyer等人(Dwyer等人,Circulation 2001,103(24),2922)评价了氧化的类胡萝卜素对通过超声检查确定的普通颈动脉的IMT的进展的保护效应,并且得到结论:增加的黄体素的膳食摄取对于对抗早期动脉粥样硬化的发展是有保护性的。这些研究结果提示,这些类胡萝卜素化合物在动脉粥样硬化的早期可能是重要的。人主动脉内皮细胞与 β -胡萝卜素、黄体素和番茄红素的预孵育分别以29、28和13%显著降低VCAM-1表达。与 β -胡萝卜素和黄体素的预孵育分别以38和34%显著降低E-选择素表达。用 β -胡萝卜素、黄体素和番茄红素预处理分别以11、14和18%显著降低ICAM-1的表达(Martin KR等人,Atherosclerosis 2000年6月;150(2):265)。患有CVD的患者倾向于具有较低的类胡萝卜素的血浆水平(Lidebjer C等人,Nutr Metab Cardiovasc

Dis 2007年7月;17(6):448)。

[0012] Rinaldi等人已经在患有轻度认知障碍(mild cognitive impairment)和患有阿尔茨海默病的受试者中,观察到抗氧化剂类胡萝卜素的低水平(Rinaldi P等人Neurobiol Aging 2003年11月;24(7):915)。的确,叶黄素如黄体素和玉米黄质可以跨越血-视网膜屏障以优先在神经视网膜的黄斑区域积累。它们还在脑组织中积累。近来,Vishwanathan将叶黄素的视网膜水平与在小脑和额叶皮质中测量的水平相关联(Vishwanathan R等人,Nutr Neurosci2013,16(1),21-)。

[0013] 在人血清中发现的十种类胡萝卜素中,在人视网膜中仅发现两种,反式-和/或内消旋-玉米黄质和黄体素。玉米黄质是黄斑中央或中心凹区中的主要类胡萝卜素并且在视网膜中心的视锥细胞,即小凹中集中。黄体素主要位于视杆细胞中的外周视网膜中。因此,相比于黄体素,眼在黄斑中央中优先吸收玉米黄质,其是比黄体素更有效的单线态氧清除剂。已经从理论上说明,由于其猝灭单线态氧并清除游离自由基的能力,玉米黄质和黄体素在视网膜中集中,并且由此限制或预防对视网膜的光损伤。

[0014] 已知的确进入视网膜的不同于玉米黄质和黄体素的类胡萝卜素可以引起副作用,如通过角黄素形成晶体沉积,其可能花数年来溶解。视网膜中的角黄素也引起降低的暗适应。

[0015] 由于其抗氧化性质,通常使用维生素(A,E或C),锌,硒,花青素或黄斑色素,如,例如,黄体素和玉米黄质。黄体素和玉米黄质是黄斑色素,代表了黄斑中的总色素的99%,其属于类胡萝卜素家族,并且具体属于叶黄素家族。两种色素一方面可以通过其吸收特别对感光体有侵略性的蓝光的能力呈现直接的保护性抗氧化效应,并且另一方面呈现直接清除自由基的抗氧化性质。US2005/0032914,US2010/0159029和W02009/129859描述了用于口服施用的组合物,其包含黄体素和玉米黄质,与其他非酶抗氧化性产品组合,用于增强视功能,抑制黄斑变性或促进眼健康。US2007/265351描述了叶黄素组合物,其包含黄体素和玉米黄质,可用于眼部健康。

[0016] 此外,黄体素被Afssa(Agence Francaise de Securite Sanitaire des Aliments)定义为“促进保护视网膜和晶状体免于氧化的药剂”(Saisine n°2003-SA-0205,2004)并且科学研究已经显示黄体素/玉米黄质的膳食摄取和患有AMD的可能性之间的关系(SanGiovanni等人,AREDS report n°22,Arch Ophthalmol,2007)。

[0017] 近来,已经表明,老化的眼具有减少的沉积在视网膜的中心凹区上的类胡萝卜素的量。临床和实验室研究表明,光损伤是年龄相关性黄斑变性的至少一个原因,因为重复的光损伤的积累效应导致感光细胞的逐步丧失和黄斑组织的变性。

[0018] 年龄相关性黄斑变性(AMD)是视网膜的不可逆致盲疾病。不同于白内障可以通过替换患病的晶状体来修复,年龄相关性黄斑变性不能通过替换患病的视网膜来治疗,因为视网膜是中枢神经系统的组成部分。由于一旦感光体被破坏则对于该疾病没有治疗手段存在,因此,预防是解决年龄相关性黄斑变性的最有效方式。目前,年龄相关性黄斑变性的预防在于限制或预防光和氧诱导的(即,游离自由基诱导的)对视网膜的损伤,因为视网膜是仅有的连续暴露于高度氧化的环境中的高水平的光的器官。

[0019] AMD是老年人中严重的、不可逆视力丧失的主要原因(Bressler,JAMA291:1900-1(2004))。其表征为广谱的临床和病理研究结果,如被称为玻璃疣的浅黄色斑点,视网膜色

素上皮(RPE)的破坏,脉络膜新生血管形成(CNV),和盘状黄斑变性。疾病的表现被分为两种形式:非渗出性(干性)和渗出性(湿性或新生血管的)。玻璃疣是干性形式的特征性损伤,而新生血管形成是湿性形式的特征。盘状AMD是新生血管损伤的纤维化阶段。

[0020] 随年龄的增加,AMD的发病率急剧增加。参见,例如Leibowitz等人,Surv Ophthalmol 24(Suppl):335-610(1980)和Klein等人,Ophthalmology99:933-43(1992)。尽管湿性形式的AMD更少见,但其是造成80%-90%的与AMD相关的严重视力损失的原因(Ferris等人,Arch Ophthalmol102:1640-2(1984))。估计有100-120万湿性AMD的发病病例。AMD的原因未知;然而,清楚的是,发展为AMD的风险随增加的年龄而增加。其他已知风险因素包括家族史和吸烟。假设的风险因素还包括氧化应激、糖尿病、酒精摄入和阳光暴露。D'Amico,N Engl J Med 331:95-106(1994)和Christen等人,JAMA276:1147-51(1996)。

[0021] 干性AMD特征为RPE和布鲁赫膜的变化。认为RPE(由年龄和其他风险因素折衷)将脂褐质和细胞碎片沉积在布鲁赫膜上。这些变化可以在眼检镜下(ophthalmoscopically)看到为玻璃疣,其可以在黄斑和视网膜后极处处散开。还存在可变的RPE的萎缩和着色程度。干性AMD可以是对称的或伴有可变的并且通常最小的视力损失,并且被认为是发展为湿性AMD的前兆。

[0022] 湿性AMD通常特征为黄斑区域的CNV。脉络膜毛细血管增殖并穿透布鲁赫膜,到达RPE并且可以延伸入视网膜下空间。新形成的毛细血管的增加的渗透性导致浆液或血液在RPE和/或感觉神经视网膜下或感觉神经视网膜内积累。当小凹变得膨胀或分离时,视力开始下降。纤维状组织转化和机化可以随之发生,导致升高的视网膜下肿块,称为盘状瘢痕,其构成末期AMD并且与持久视力丧失相关(D'Amico DJ.N Engl J Med331:95-106(1994))。基于小凹下脉络膜新生血管性病变的荧光素血管造影术,AMD中的新血管形成可以归类为不同模式。TAP和VIP研究组,Arch Ophthalmol 121:1253-68(2003)。主要的血管造影模式被称为经典的和隐匿的并且与不同程度的侵蚀性、视力损失和对不同治疗选择的响应相关。

[0023] 叶黄素组包括(在很多其他化合物中)黄体素,玉米黄质,新黄素,紫黄质,以及 α -和 β -隐黄素。后一化合物是仅有的含有 β -紫罗酮环的已知叶黄素,并且因此 β -隐黄素是用于哺乳动物的已知具有前维生素A活性的仅有的叶黄素。尽管那样,其是仅用于具有从含有 β -紫罗酮的类胡萝卜素制造视黄醛的酶的食草哺乳动物的维生素(一些食肉动物缺乏该酶)。在除了哺乳动物之外的物种中,某些叶黄素可以转变为羟化的视黄醛-类似物,其在视觉中直接行使功能。例如,除了某些蝇类外,多数昆虫使用3-羟基视黄醛的叶黄素衍生的R-异构体用于视觉活动,其意为 β -隐黄素和其他叶黄素(如黄体素和玉米黄质)可以以它们的视觉“维生素A”的形式起作用,而胡萝卜素(如 β 胡萝卜素)不是。

[0024] 在人中,根据Kaplan等人(Clin Physiol Biochem 1990,8,1)和Schmitz等人(J Nutr 1991,121,1613),黄体素和玉米黄质在亲脂组织中积累并且由脂蛋白运出。

[0025] 类胡萝卜素的肠吸收和组织分布。最可能是由于它们的亲脂性,类胡萝卜素的吸收和分布是复杂的并且是高度可变的(Castenmiller,J.J.Annu Rev Nutr 1998;18:19)。其涉及肠组分胆汁酸,酶如酯酶,肠上皮细胞中的受体并且向脂蛋白中的包含,血浆或淋巴中的分泌和在脂蛋白之间分布及向组织的递送。Greene等人(Greene,C.M.Nutr Metab(Lond) 2006;3:-6)注意到黄体素和玉米黄质血浆浓度与HDL尺寸之间的关系,并且推测,由于它们

在脂蛋白表面处的位置,在HDL与其他脂蛋白相互作用时,这些类胡萝卜素可以在粒子重建过程中交换。此外,遗传变异参与类胡萝卜素生物利用度的个体间差异,如Borel(Borel, P.Mol Nutr Food Res 2012February;56(2):228)所综述的,他建议了根据个体遗传特性的个性化的对于类胡萝卜素的膳食指南。已经发表了多个利用不同制剂增加黄体素的生物利用度的尝试。尽管来自蛋的利用度似乎可以满足,但同时增加血浆胆固醇可能在一些患者中是不合适的(Thurnham,D.I.Nutr Res Rev 2007December;20(2):163)。

[0026] ABCA1和前-βHDL在小肠吸收中的具体作用。已经在具有Z-连锁突变的鸡中描述第一个HDL缺陷综合征的动物模型(Poernama,F.J Lipid Res1990June;31(6):955),之后发现影响ABCA1功能。Attie等人(Attie,A.D.J Lipid Res 2002年10月;43(10):1610}鉴定了WHAM鸡的ABCA1基因中的E89K突变并且该动物模型提供了直接证据证明ABCA1调节胆固醇从肠上皮细胞的基底外侧表面向前-β/低脂化的ApoA1的流出(Mulligan,J.D.J Biol Chem 2003April 11;278(15):13356)。前-βHDL的作用非常可能是肠水平的叶黄素摄取的限速步骤,因为成熟HDL的注射不补偿天然低脂化的apoA1的缺少(Mulligan,J.D.J Biol Chem 2003April 11;278(15):13356)。我们猜测,通过CETP活性有效重建为前-βHDL的HDL(Niesor,E.J.2010J Lipid Res 2010December;51(12):3443)参与天然HDL通过肠上皮细胞肠脂化的过程,并且痕量的植物来源的固醇(植物甾醇)也由该过程摄取(Niesor, E.J.Atherosclerosis 2011年12月;219(2):761)。我们之前表明,CETP是人血浆中HDL重建和前-β-HDL形成的主要成分,并且CETP调节剂如达塞曲匹可以增强参与HDL重建的CETP活性(Niesor,E.J.2010J Lipid Res 2010年12月;51(12):3443)。这将导致增加血浆中的前-βHDL形成,肠上皮细胞基底侧面ABCA1导致的脂化,并且最终增加类胡萝卜素吸收。利用非选择性/完全CETP抑制剂如托斯瑞比(torcetrapib),未观察到该现象。同样的发生在视网膜水平的前-βHDL的增加可以增加过量胆固醇和氧化的脂质的流出,如Ishida等人描述的(Ishida,B.Y Br J Ophthalmol 2006年5月;90(5):616)。

[0027] 根据本发明已经发现,不是所有CETP抑制剂都可用于增加血浆和组织叶黄素,从而预防、治疗眼疾病和或延迟眼疾病进展和/或减少眼疾病,所述眼疾病如白内障、角膜混浊(浑浊化)、青光眼、葡萄膜炎、眼内新生血管性疾病,尤其是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞(CRVO)、角膜新生血管形成、视网膜新生血管形成、年龄相关性黄斑变性(AMD)。CETP调节剂如S-[2-[1-(2-乙基丁基)环己基羰基氨基]-苯基]2-甲基硫代丙酸酯可用于预防、治疗和/或减少眼疾病,特别是AMD。

[0028] 的确证明的是,已经开发了来自两种不同化学类型的CETP抑制剂并且到达晚期临床开发。第一类是有效的CETP抑制剂,其是3,5-双-三氟甲基-苯衍生物如托斯瑞比(Clark RW,Arterioscler Thromb Vasc Biol.2004;24(3):490-7)和安塞曲匹(anacetrapib),已经显示其以高至130%升高人中血浆HDL-C((Krishna R,Clin Pharmacol Ther.2008年12月;84(6):679-83.))。因为由与CETP抑制不相关(Forrest MJ,Br J Pharmacol.2008;154(7):1465-73.,Hu X,Endocrinology.2009;150(5):2211-9,)的脱靶效应导致的增加的CV和非-CV死亡和事件(Barter PJ,N Engl J Med.2007;357(21):2109-22),托斯瑞比的III期致死/发病率研究过早终止。第二化学类型是“CETP调节剂”如苯硫酚衍生物,由S-[2-[1-(2-乙基丁基)环己基羰基氨基]-苯基]2-甲基硫代丙酸酯代表,其在600mg的剂量以高达

36%升高人中HDL-C(Stein EA, Am J Cardiol. 2009;104(1):82-91.)并且由于对于CVD患者无效而在III期结果研究中终止。

[0029] 除了效力之外,从两种化学类型衍生的化合物导致的CETP抑制的机制也可能不同。托斯瑞比对CETP的结合增加其对脂蛋白的亲合力,并且诱导CETP和脂蛋白如HDL之间的失活高亲和复合体的形成(Clark RW, J Lipid Res 2006;47:537-552)。CETP-脂蛋白复合体,与由CETP抑制剂抗体TP2诱导的复合体(Swenson TL, J Biol Chem 1989;264:14318-26.)类似,不能有效在不同脂蛋白颗粒之间进行神经脂交换。尽管CETP调节剂如S-[2-[1-(2-乙基丁基)环己基羰基氨基]-苯基]2-甲基硫代丙酸酯减小CETP活性的准确机制尚未阐明,已经提示作用模式包括CETP的半胱氨酸13(Cys13)和1-(2-乙基-丁基)-环己烷甲酸(2-巯基-苯基)-酰胺(S-[2-[1-(2-乙基丁基)环己基羰基氨基]-苯基]2-甲基硫代丙酸酯的活性代谢物,其在胃肠道中和在血浆中由非特异性酯酶裂解)的苯硫酚部分之间的直接特异相互作用,从而允许与CETP形成二硫键(Okamoto H, Nature 2000;406(6792):203-207)。

[0030] 有兴趣区分两种类型的化合物,因为似乎它们具有不同的作用机制。因此存在在体外或活体外将CETP调节剂如S-[2-[1-(2-乙基丁基)环己基羰基氨基]-苯基]2-甲基硫代丙酸酯,双[2-[1-(2-乙基丁基)环己基羰基氨基]苯基]二硫化物或1-(2-乙基-丁基)-环己烷甲酸(2-巯基-苯基)-酰胺和其前药衍生物与所有其他CETP抑制剂,尤其是有效的CETP抑制剂如3,5-双-三氟甲基-苯衍生物(即托斯瑞比和安塞曲匹)区分的需要。

[0031] 因此CETP调节剂定义为降低CETP的胆固醇酯转移活性并且增加CETP诱导的HDL重建(导致增强的前- β /新生HDL颗粒水平)的化合物(Niesor JLR和Maugeais等人BBA Lipids)。

[0032] 除非另有说明,说明书和权利要求中使用的以下术语具有下文给出的意义:

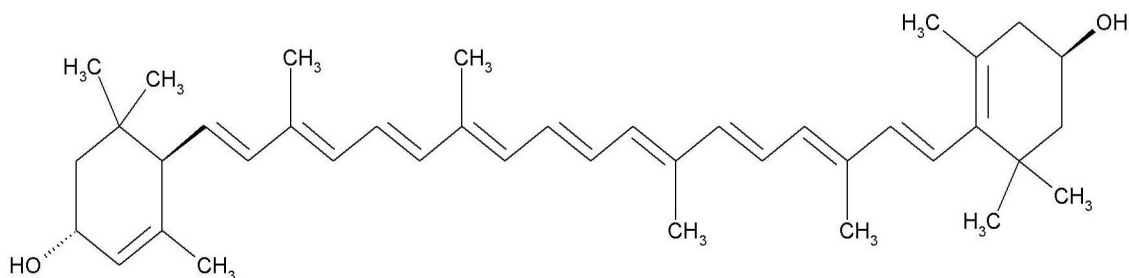
[0033] 如本文使用的,单数形式“一个(a)”,“一个(an)”,和“那个(the)”包括复数对象,除非内容明确另有指示。因此一种化合物任选地包括两种或多种这样的化合物的组合,等。

[0034] “CETP调节剂”是指通过在结合CETP多肽时诱导CETP多肽的构象变化而调节CETP活性(通过标准转移测定评估)的化合物,其中构象变化如下文所述测量。该特异相互作用允许CETP的胆固醇酯转移活性在HDL颗粒之间进行并且增加CETP诱导的新生前- β HDL的产生。优选地,CETP调节剂是指所有会结合CETP多肽的半胱氨酸13的化合物。更优选地,“CETP调节剂”选自S-[2-[1-(2-乙基丁基)环己基羰基氨基]-苯基]2-甲基硫代丙酸酯、1-(2-乙基-丁基)-环己烷甲酸(2-巯基-苯基)-酰胺和或双[2-[1-(2-乙基丁基)环己基羰基氨基]苯基]二硫化物。最优选地,“CETP调节剂”是作为前药的S-[2-[1-(2-乙基丁基)环己基羰基氨基]-苯基]2-甲基硫代丙酸酯或作为其活性代谢物的1-(2-乙基-丁基)-环己烷甲酸(2-巯基-苯基)-酰胺。

[0035] 术语“稀释剂”是指充满片剂或胶囊的尺寸,使其适于生产并且方便消费者使用的赋形剂。合适的稀释剂包括例如药用填料,如微晶纤维素(例如Avicel[®])、微粒化的交聚维酮、纤维素粉末、喷雾干燥的乳糖、无水乳糖、一水合乳糖、磷酸氢钙、糖、糖醇、玉米淀粉、淀粉、预胶化的淀粉、胶体二氧化硅、多糖和其混合物。

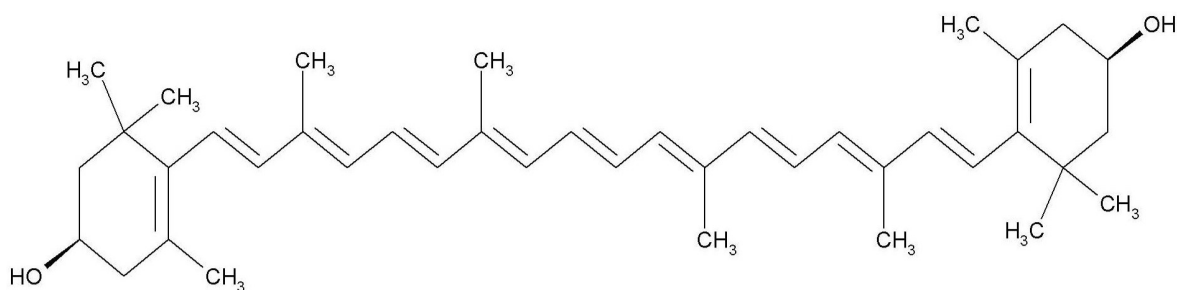
[0036] 黄体素由植物合成并且发现在绿叶蔬菜如菠菜和羽衣甘蓝中是大量的。黄体素化学结构是:

[0037]



[0038] 黄体素(CAS登记号127-40-2)也称为(3R,3'R,6'R)- β , ϵ -胡萝卜素-3,3'-二醇,玉米黄质(CAS登记号144-68-3),也称为(3R,3'R)- β , β -胡萝卜素-3,3'-二醇,具有以下化学结构:

[0039]



[0040] 玉米黄质存在于玉米、藏红花、西方雪果中。

[0041] 术语“有效量”或“治疗有效量”是指有效治疗哺乳动物中疾病或病症的药物的量。在年龄相关性黄斑变性(AMD)的情况下,药物的有效量可以减少或预防视力损失。对于AMD治疗,体内效力可以,例如,通过以下各项的一种或多种测量:评价相对于所希望的时间从基线最佳校正的视敏度(BCVA)的平均变化,评价与基线相比在所希望的时间视敏度损失少于15个字母(letter)的受试者的比例,评价与基线相比在所希望的时间视敏度增加大于或等于15个字母的受试者的比例,评价在所希望的时间具有20/2000的视敏度Snellen当量或更差的受试者的比例,评价NEI视觉功能问卷,评价在所希望的时间的CNV尺寸和CNV渗漏的量,如通过荧光素血管造影术等评价的。“治疗剂量”是对患者呈现治疗效果的剂量并且亚治疗剂量是对治疗的患者未呈现治疗效果的剂量。

[0042] “眼内新生血管性疾病”是特征在于眼新生血管形成的疾病。眼内新生血管性疾病的实例包括,但不限于,例如,增生性视网膜病变,脉络膜新生血管形成(CNV),年龄相关性黄斑变性(AMD),糖尿病和其他缺血相关视网膜病变,糖尿病性黄斑水肿,病理性近视,脑视网膜血管瘤病,眼组织胞浆菌病,视网膜中央静脉阻塞(CRVO),角膜新生血管形成,视网膜新生血管形成等。

[0043] 术语“抗体”包括各种形式的抗体结构,包括但不限于全抗体和抗体片段。根据本发明的抗体优选地为人源化抗体、嵌合抗体,或进一步遗传改造的抗体,只要抗体结合CETP多肽的表位,其中所述表位仅以CETP:CETP调节剂复合体形式或CETP天然形式对于抗体是可接近的(暴露的)。

[0044] “抗体片段”包括全长抗体的一部分,优选其可变结构域,或至少其抗原结合位点。

抗体片段的实例包括双抗体(diabodies)、单链抗体分子、和由抗体片段形成的多特异性抗体。scFv抗体是例如在Houston, J.S., *Methods in Enzymol.* 203(1991)46-96)中所描述的。

[0045] 本文使用的术语“单克隆抗体”是指单一氨基酸组成的抗体分子的制剂。

[0046] 术语“表位”包括能够特异结合抗体的任何多肽决定簇。在某些实施方案中,表位决定簇包括分子的化学活性的表面基团(grouping),如氨基酸、糖侧链、磷酸基、或磺酰基,并且,在某些实施方案中,可以具有特定的三维结构特性和或特定的电荷特性。表位是抗原被抗体结合的区域。

[0047] “CETP:CETP调节剂复合体”是指如本文所述的CETP多肽与CETP调节剂的复合。优选地,“CETP:CETP调节剂复合体”由CETP多肽与结合半胱氨酸13或其他游离半胱氨酸,优选如本文所述的结合CETP多肽的半胱氨酸13的化合物接触而造成。

[0048] 术语“结合(binding)”或“结合(bind to)”是指两个分子种类之间的特异缔合或其他特异相互作用,如蛋白-蛋白或蛋白-小分子相互作用。考虑的是该缔合通过两个相互作用的分子种类中的每个上的特异结合位点介导。

[0049] 术语“结合位点”是指一个分子直接参与其与另一分子的特异结合的反应区或结构域。例如,当涉及蛋白上的结合位点时,由于与其他分子相互作用的特定氨基酸序列的存在而发生结合。

[0050] 术语“吸湿性聚合赋形剂”意为吸取水分的聚合赋形剂,例如通过甚至在低至50%的相对湿度,在室温(例如约25℃)的吸收或吸附。水分摄取是例如通过动态蒸气吸附在室温测量的。作为实例,吸湿性可以根据欧洲药典-第6版(2008),第5.11章中所公开的方法测量。动态蒸气吸附技术测量由改变产品周围的蒸气浓度产生的质量上的变化。合适的“吸湿性聚合赋形剂”是羟丙基甲基纤维素、羟丙基纤维素、低取代羟丙基纤维素、羟乙基甲基纤维素、羧基聚亚甲基、甲基纤维素、乙基纤维素、羟乙基纤维素、醋酸纤维素、聚乙烯吡咯烷酮交联的聚乙烯吡咯烷酮、微粒化的交联的聚乙烯吡咯烷酮、羧甲基纤维素钠、羧甲基纤维素钙、交联的羧甲基纤维素、微晶纤维素、硅化的微晶纤维素、纤维素粉末、羧甲基淀粉、淀粉、预胶化的淀粉或其混合物。尤其是,“吸湿性聚合赋形剂”是指羟丙基甲基纤维素、羧甲基纤维素钠、微晶纤维素和微粒化的交联的聚乙烯吡咯烷酮。在室温(例如约25℃)“不溶于水的吸湿性聚合物”的实例包括低取代羟丙基纤维素、羧基聚亚甲基、乙基纤维素、醋酸纤维素、交联聚乙烯吡咯烷酮、微粒化的交联的聚乙烯吡咯烷酮、羧甲基纤维素钙、微晶纤维素、硅化的微晶纤维素、纤维素粉末和淀粉。

[0051] 术语“超级崩解剂”是指在与水接触时非常快速展开的崩解剂。通常而言,超级崩解剂是可以以正常崩解剂的零头使用以获得相同效果的崩解剂。超级崩解剂的实例包括交联的羧甲基纤维素钠(也称为交联羧甲基纤维素钠(croscarmellose sodium)),淀粉羟乙酸钠,和交联聚乙烯吡咯烷酮(也称为交聚维酮)。交联羧甲基纤维素钠可从FMC公司以商品名 **Ac-Di-Sol®** 市购和从Avebe公司以商品名 **Primellose®** 市购。淀粉羟乙酸钠可从Penwest Pharmaceuticals Co.以商品名 **Explotab®** 市购和从Avebe公司以商品名 **Primojel®** 市购。交聚维酮可从BASF公司以商品名 **Kollidon®** CL市购和从International Specialty Chemicals公司以商品名 **Polyplasdone®** 市购。交联羧甲基纤维素钠还可从

Mingtai Chemical Co.Ltd以商品名DISOLCEL[®]和从J.Rettenmaier&SöhneGmbH+Co (JRS)以商品名Vivasol[®]市购。最优选的超级崩解剂是交联羧甲基纤维素钠和交聚维酮。

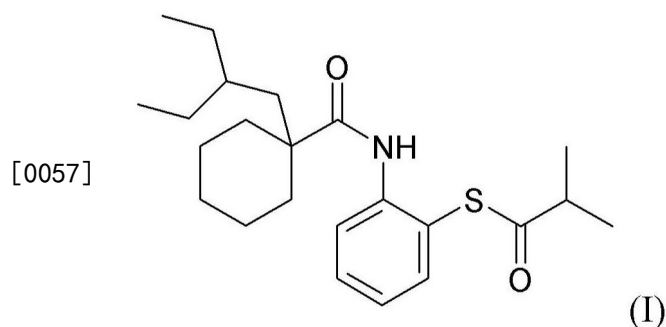
[0052] 术语“水不稳定的”意为存在水解敏感性官能团如酯、酰胺或硫酯。

[0053] 在本发明的特定实施方案中,本发明显示CETP调节剂与一种或多种类胡萝卜素,更特别是与一种或多种类叶黄素如黄体素,反式-玉米黄质,内消旋-玉米黄质和虾青素(单独或其组合)的组合在预防、治疗眼疾病、延迟眼疾病的进展和/或减少眼疾病方面的阳性相互作用,所述眼疾病如白内障,角膜混浊(浑浊化),青光眼,葡萄膜炎,眼内新生血管性疾病,尤其是增生性视网膜病变,脉络膜新生血管形成(CNV),糖尿病性及其他缺血相关视网膜病变,糖尿病性黄斑水肿,病理性近视,脑视网膜血管瘤病,眼组织胞浆菌病,视网膜中央静脉阻塞(CRVO),角膜新生血管形成,视网膜新生血管形成,年龄相关性黄斑变性(AMD),更特别是AMD,最特别是干性AMD。

[0054] 在本发明的特定实施方案中,本发明显示CETP调节剂与一种或多种类胡萝卜素,更特别是与一种或多种类叶黄素如黄体素,反式-玉米黄质,内消旋-玉米黄质和虾青素(单独或其组合)的组合在预防、治疗眼疾病、延迟眼疾病的进展和/或减少眼疾病方面的协同作用,所述眼疾病如白内障,角膜混浊(浑浊化),青光眼,葡萄膜炎,眼内新生血管性疾病,尤其是增生性视网膜病变,脉络膜新生血管形成(CNV),糖尿病性及其他缺血相关视网膜病变,糖尿病性黄斑水肿,病理性近视,脑视网膜血管瘤病,眼组织胞浆菌病,视网膜中央静脉阻塞(CRVO),角膜新生血管形成,视网膜新生血管形成,年龄相关性黄斑变性(AMD),更特别是AMD,最特别是干性AMD。

[0055] 除非另有陈述,所有百分数以组合物的总重量的重量百分数给出。

[0056] 在特定实施方案中,“CETP调节剂”是硫代异丁酸S-(2-[[1-(2-乙基-丁基)-环己烷羰基]-氨基]-苯基)酯,也称为S-[2-([[1-(2-乙基丁基)-环己基]-羰基]氨基)苯基]2-甲基硫代丙酸酯,达塞曲匹或式I的化合物



[0058] 已经显示在人(de Grooth等人,Circulation,105,2159-2165(2002))和兔(Shinkai等人,J.Med.Chem.,43,3566-3572(2000);Kobayashi等人,Atherosclerosis,162,131-135(2002);和Okamoto等人,Nature,406(13),203-207(2000))中,S-[2-([[1-(2-乙基丁基)环己基]羰基]氨基)苯基]2-甲基硫代丙酸酯是CETP活性的调节剂。已经显示S-[2-([[1-(2-乙基丁基)环己基]羰基]氨基)苯基]2-甲基硫代丙酸酯增加人(de Grooth等人,见上)和兔(Shinkai等人,见上;Kobayashi等人,见上;Okamoto等人,见上)中血浆HDL胆固醇。此外,已经显示在人(de Grooth等人,见上)和兔(Okamoto等人,见上)中S-[2-([[1-(2-乙基丁基)环己基]羰基]氨基)苯基]2-甲基硫代丙酸酯降低LDL胆固醇。S-[2-([[1-(2-

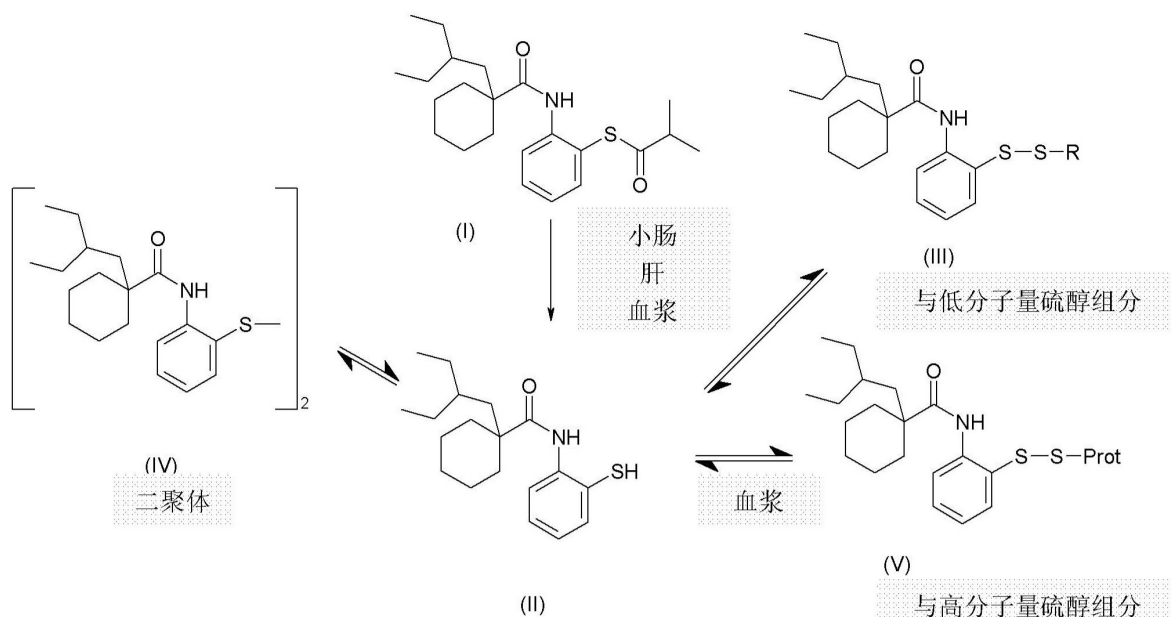
乙基丁基)环己基]羰基]氨基)苯基]2-甲基硫代丙酸酯,以及制备和使用所述化合物的方法,在欧洲专利EP1020439,Shinkai等人,J.Med.Chem.43:3566-3572(2000)或W0 2007/051714,W0 2008/074677或W02011/000793中描述。

[0059] 在优选的实施方案中,CETP调节剂(例如式I的化合物)是结晶或无定形固体,更优选是结晶形式。在特定实施方案中,S-[2-([1-(2-乙基丁基)-环己基]-羰基]氨基)苯基]2-甲基硫代丙酸酯是晶型A。

[0060] 晶型A的特征是在约 7.9° , 8.5° , 11.7° , 12.7° , 17.1° , 18.0° , 18.5° , 20.2° , 22.1° , $24.7^\circ \pm 0.2^\circ$ 具有峰的X-射线粉末衍射图,尤其是在 7.9° , 11.7° , 17.1° , $18.5^\circ (\pm 0.2^\circ)$ 的衍射角 2θ 观察到的XRPD峰。

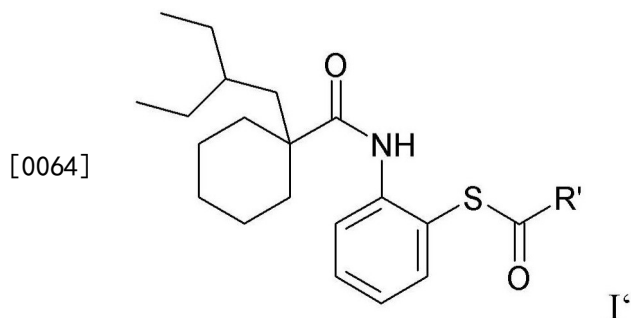
[0061] 不希望受限于任何特定理论,猜测在患者体内,化合物I在血浆、肝和/或小肠中水解,形成S-[2-([1-(2-乙基丁基)-环己基]-羰基]氨基)苯基]硫醇(本文也称为化合物II)。已知,低分子量硫醇组分(即,R-SH),如半胱氨酸和谷胱甘肽,和高分子量硫醇组分(即,Prot-SH),如肽和蛋白(例如,酶和细胞膜),作为在分子间或分子内含有氧化的二硫键10(S-S键)的混合二硫化物存在于体内(参见,例如,Shimada等人,J Chromatogr.B,659,227(1994))。因此,猜想在患者体内,化合物II与低或高分子量硫醇缀合产生混合的二硫化物或产生化合物II的二聚体。因为这些形式经由化合物II彼此处于氧化还原平衡,所有这些形式,以及化合物II,在下文共同地(但非排他地)被认为或称为化合物I的活性形式。下述图表描述了上述的猜想。

[0062]



[0063] 尽管施用化合物I是本发明的特别优选的实施方案,本发明还考虑施用将产生化合物I的活性形式的其他化合物,即,化合物I的活性形式的其他前药。这样的前药,例如,可以是具有不同的巯基-保护基团,但仍然导致在患者体内(即,体内)形成化合物I的活性形式(例如,化合物II)的化合物。术语“巯基-保护基团”是指通常使用的巯基-保护基团(例如,如在Wolman, The Chemistry of the Thiol Group, D. Patai, Ed., Wiley-Interscience, New York, 1974中所述的)。可以使用可以在体内解离的任何有机残基而没有特别限制。特别合适的巯基-保护基团的实例在美国专利6,426,365中描述。本发明还考

考虑施用化合物I' (其中R' 意为除异丙基之外的有机残基)以产生化合物I的活性形式。



[0065] 此外,据信与化合物II在体内平衡的化合物III,IV和V(其中R表示有机残基并且Prot表示肽或蛋白),可类似地直接施用于患者。

[0066] 评估胆固醇酯转移蛋白(CETP)的构象变化的方法可以包括:

[0067] -从用CETP调节剂治疗的患者采集血浆样品,其中CETP调节剂结合于CETP多肽内的表位,其诱导构象变化;

[0068] -测量抗体结合或不结合CETP:CETP调节剂复合体的能力,其中抗体结合CETP多肽的表位,其中所述表位仅以CETP:CETP调节剂复合体形式或CETP天然形式可接近(暴露)于抗体。尤其是抗体可以是JHC 1。JHC-1抗体可以获自Japan Tobacco。

[0069] 抗体可以根据Takahashi H,Biochem Biophys.Res.Commun 2001,27,283,118的公开内容,使用针对从脂蛋白-消耗的健康人血浆通过苯基Sepharose HP柱(Amersham Pharmacia Biotech)和Resource Q柱(Amersham Pharmacia Biotech)色谱部分纯化的CETP免疫的Balb/c小鼠产生。

[0070] 其他抗体根据Davis等人1998年,在用20μg的在含有CPG-OGN的氢氧化铝凝胶(Alhydrogel-2%,Brenntag Biosector)中乳化的rhCETP腹膜注射的Naval Medical Research Institute(NMRI)小鼠中产生。动物以3周间隔接受相同抗原制剂的四次加强注射。

[0071] 动物一显示对重组人CETP(rhCETP)的特异免疫应答,就用最佳响应剂(responders)加强并且3天后,移除脾并将分离的细胞融合于PAI骨髓瘤细胞(P3-x63-AG8骨髓瘤的变体)(Köhler&Milstein 1975)。选择以下单克隆抗体用于进一步表征:6/2,6/6 6/17。

[0072] 尽管在下文的实施例中使用6/6作为内部检测抗体/缀合抗体,其可以容易地用来自上述参考文献的JHC2替换。该抗体可以以与Takahashi H,Biochem Biophys.Res.Commun 2001,27,283,118中公开的步骤类似的方式产生。

[0073] -更特别地,评价构象变化的方法可以是酶联免疫吸附测定(ELISA)方法。例如ELISA方法可以如下进行:

[0074] --将用CETP调节剂治疗的患者的血浆样品的溶液施用在抗体,尤其是JHC1或6/2上,

[0075] -孵育,

[0076] -冲洗多余的,

[0077] -施用缀合的抗体,尤其是JHC 2或6/6的溶液,

[0078] -猝灭反应,

[0079] -测量光密度。

[0080] 备选地,构象改变的方法可以在Okamoto H,Nature 2000;406(6792):203-207中找到。

[0081] 在特定实施方案中,本发明涉及“CETP调节剂”,其可用于预防眼疾病如白内障、角膜混浊(浑浊化)、青光眼、葡萄膜炎、眼内新生血管性疾病,尤其是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞(CRVO)、角膜新生血管形成、视网膜新生血管形成、年龄相关性黄斑变性(AMD),更特别是AMD,最特别是干性AMD。

[0082] 在另一特定实施方案中,本发明涉及“CETP调节剂”,其可用于治疗眼疾病如白内障、角膜混浊(浑浊化)、青光眼、葡萄膜炎、眼内新生血管性疾病,尤其是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞(CRVO)、角膜新生血管形成、视网膜新生血管形成、年龄相关性黄斑变性(AMD),更特别是AMD,最特别是干性AMD。

[0083] 在另一特定实施方案中,本发明涉及“CETP调节剂”,其可用于延迟眼疾病的进展,所述眼疾病如白内障、角膜混浊(浑浊化)、青光眼、葡萄膜炎、眼内新生血管性疾病,尤其是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞(CRVO)、角膜新生血管形成、视网膜新生血管形成、年龄相关性黄斑变性(AMD),更特别是AMD,最特别是干性AMD。

[0084] 在另一特定实施方案中,本发明涉及“CETP调节剂”,其可用于减少眼疾病如白内障、角膜混浊(浑浊化)、青光眼、葡萄膜炎、眼内新生血管性疾病,尤其是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞(CRVO)、角膜新生血管形成、视网膜新生血管形成、年龄相关性黄斑变性(AMD),更特别是AMD,最特别是干性AMD。

[0085] 在另一实施方案中,本发明包括“CETP调节剂”,其用作治疗活性物质,用于治疗眼疾病如白内障、角膜混浊(浑浊化)、青光眼、葡萄膜炎、眼内新生血管性疾病,尤其是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞(CRVO)、角膜新生血管形成、视网膜新生血管形成、年龄相关性黄斑变性(AMD),更特别是AMD,最特别是干性AMD。

[0086] 在另一实施方案中,本发明包括“CETP调节剂”,其用作治疗活性物质,用于预防眼疾病如白内障、角膜混浊(浑浊化)、青光眼、葡萄膜炎、眼内新生血管性疾病,尤其是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞(CRVO)、角膜新生血管形成、视网膜新生血管形成、年龄相关性黄斑变性(AMD),更特别是AMD,最特别是干性AMD。

[0087] 在另一实施方案中,本发明包括“CETP调节剂”,其用作治疗活性物质,用于延迟眼

疾病的进展,所述眼疾病如白内障、角膜混浊(浑浊化)、青光眼、葡萄膜炎、眼内新生血管性疾病,尤其是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞(CRVO)、角膜新生血管形成、视网膜新生血管形成、年龄相关性黄斑变性(AMD),更特别是AMD,最特别是干性AMD。

[0088] 在另一实施方案中,本发明包括“CETP调节剂”,其用作治疗活性物质,用于减少眼疾病如白内障、角膜混浊(浑浊化)、青光眼、葡萄膜炎、眼内新生血管性疾病,尤其是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞(CRVO)、角膜新生血管形成、视网膜新生血管形成、年龄相关性黄斑变性(AMD),更特别是AMD,最特别是干性AMD。在特定实施方案中,本发明包括药物组合物,其包含胆固醇酯转移蛋白调节剂如5-[2-([1-(2-乙基丁基)环己基]羰基]氨基)苯基]2-甲基硫代丙酸酯和交聚维酮,可用于预防眼疾病、治疗眼疾病、延迟眼疾病进展和/或减少眼疾病,所述眼疾病如白内障、角膜混浊(浑浊化)、青光眼、葡萄膜炎、眼内新生血管性疾病,尤其是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞(CRVO)、角膜新生血管形成、视网膜新生血管形成、年龄相关性黄斑变性(AMD),更特别是AMD,最特别是干性AMD。

[0089] 在本发明的另一实施方案中,本文所述的组合物是药物组合物,尤其可用于预防眼疾病如白内障、角膜混浊(浑浊化)、青光眼、葡萄膜炎、眼内新生血管性疾病,尤其是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞(CRVO)、角膜新生血管形成、视网膜新生血管形成、年龄相关性黄斑变性(AMD),更特别是AMD,最特别是干性AMD。

[0090] 在本发明的另一实施方案中,本文所述的组合物是药物组合物,尤其可用于治疗眼疾病如白内障、角膜混浊(浑浊化)、青光眼、葡萄膜炎、眼内新生血管性疾病,尤其是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞(CRVO)、角膜新生血管形成、视网膜新生血管形成、年龄相关性黄斑变性(AMD),更特别是AMD,最特别是干性AMD。

[0091] 在本发明的另一实施方案中,本文所述的组合物是药物组合物,尤其可用于延迟眼疾病的进展,所述眼疾病如白内障、角膜混浊(浑浊化)、青光眼、葡萄膜炎、眼内新生血管性疾病,尤其是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞(CRVO)、角膜新生血管形成、视网膜新生血管形成、年龄相关性黄斑变性(AMD),更特别是AMD,最特别是干性AMD。

[0092] 在本发明的另一实施方案中,本文所述的组合物是药物组合物,其尤其可用于减少眼疾病如白内障、角膜混浊(浑浊化)、青光眼、葡萄膜炎、眼内新生血管性疾病,尤其是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞

(CRVO)、角膜新生血管形成、视网膜新生血管形成、年龄相关性黄斑变性(AMD),更特别是AMD,最特别是干性AMD。

[0093] 在另一实施方案中,本发明包括治疗剂量的“CETP调节剂”,其用作治疗活性物质,用于减少眼疾病如白内障、角膜混浊(浑浊化)、青光眼、葡萄膜炎、眼内新生血管性疾病,尤其是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞(CRVO)、角膜新生血管形成、视网膜新生血管形成、年龄相关性黄斑变性(AMD),更特别是AMD,最特别是干性AMD。本文中的术语“治疗剂量”意为一种或多种化合物产生与正在治疗的疾病或病况相关的症状和状况的变化。治疗剂量产生与疾病相关的症状或状况的递增的变化就足够了;不需要治愈或完全缓和症状。本领域普通技术人员可以容易地通过根据已知方法建立用于测量治疗的疾病的症状或状况的改变的标准并且随后监测这些标准的改变,来确定一个剂量是否是治疗性的。与疾病相关的外部物理状态、患者中受影响组织的组织学检查或特定细胞或化合物的存在或不存在,可以提供评价治疗效果的客观标准。在一个实例中,本发明的方法可以用于治疗AMD,其中疗效通过在预防视力损失中的变化评价。疗效的其他指标对于本领域技术人员将是显而易见的并且可以用于建立剂量的效力。还参见本文中标题为“治疗效力”的部分。

[0094] 剂量可以根据适于治疗疾病或病况的任何时间安排施用。例如,剂量可以基于每日、每周、每两周、或每月施用,从而实现所需的疗效并减少副作用。剂量可以在发展出病症之前、期间或之后施用。特定时间安排可以由具有施用治疗性化合物方面的普通技术的医生,通过本发明的方法内的剂量给药时间安排的常规调整来确定。调节第一次个体剂量和第二次个体剂量以及随后的剂量的施用时间以最小化副作用,同时维持最大治疗效果。副作用的出现可以通过常规患者访谈监控,并且可以调整以通过调节剂量给药的时间最小化副作用的出现。例如,剂量可以以每日的方案施用。

[0095] 可用于预防、治疗眼疾病、延迟眼疾病的进展和/或减少眼疾病(所述眼疾病如白内障、角膜混浊(浑浊化)、青光眼、葡萄膜炎、眼内新生血管性疾病,尤其是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞(CRVO)、角膜新生血管形成、视网膜新生血管形成、年龄相关性黄斑变性(AMD),更特别是AMD,最特别是干性AMD)的CETP调节剂还可以用于与其他活性成分联合。例如,式(I)的化合物可以与抗VEGF化合物联合使用。

[0096] 在本说明书的情况下,“与...联合”应该被理解为共施用,或两种活性成分的组合。共施用可以是同时的、几乎同时的、或在时间上推迟数天或数周,例如多至4或5周。

[0097] 血管内皮生长因子(VEGF)是内源性分子,其参与很多生理过程,包括胎儿期、创伤愈合期间的血管生长,或用于具有缺陷的血液供应的组织中的新血管生长。VEGF还参与病理过程,如允许肿瘤生长和扩散的肿瘤血液脉管系统的发展,或最终导致视力损失的眼中新血管形成。因此,抗VEGF治疗的目的在于通过阻断VEGF作用来预防该异常血管形成。

[0098] 抗-VEGF化合物的实例包括哌加他尼钠® (Macugen®) (哌加他尼钠(Pegaptanib Sodium))、雷珠单抗(Lucentis)(雷珠单抗(ranibizumab))、阿瓦

斯丁® (Avastatin®)(贝伐单抗(bevacizumab))RhuFab、或VEGF Trap Eye。因此,在另一方面,CETP调节剂与抗VEGF化合物联合使用,用于预防、治疗和/或减少年龄相关性黄斑变性。在另一实施方案中,本发明提供CETP调节剂和一种或多种类胡萝卜素,尤其是其中所述类胡萝卜素是叶黄素,更特别是其中所述类胡萝卜素是具有任选地一种玉米黄质的立体异构体的黄体素,其用于预防、治疗眼疾病,延迟眼疾病进展和/或减少眼疾病,所述眼疾病如白内障、角膜混浊(浑浊化)、青光眼、葡萄膜炎、眼内新生血管性疾病,尤其是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞(CRVO)、角膜新生血管形成、视网膜新生血管形成、年龄相关性黄斑变性(AMD),更特别是AMD,最特别是干性AMD。

[0099] 在一个实施方案中,至少一种玉米黄质异构体选自玉米黄质和内消旋玉米黄质组成的组。在进一步实施方案中,黄体素的量范围从0.5至25mg,并且至少一种玉米黄质异构体的量范围从0.1-5mg。有利地,黄体素和至少一种玉米黄质异构体以约5:1的黄体素:玉米黄质异构体比例存在于组合物中。在优选的实施方案中,所述联合是CETP调节剂,黄体素和至少一种玉米黄质异构体的均质混合物。

[0100] 根据本发明的“CETP调节剂”或组合物用于治疗哺乳动物(即猫、狗、仓鼠、兔、小鼠、沙鼠、大鼠、豚鼠、或人,尤其是人(即男人或女人))。

[0101] 因此,本发明提供治疗或预防哺乳动物中眼疾病的方法,所述方法包括向哺乳动物(优选需要其的哺乳动物)施用治疗有效量的药物组合物。所述哺乳动物优选为人(即,男人或女人)。人可以是任何种族(例如高加索人或东方人)。眼疾病优选选自疾病或创伤引起的对视网膜的变性疾病或损伤,眼疲劳,眼的适应性机能障碍,视疲劳,糖尿病视网膜病变或干眼综合征,后者由泪或脂腺炎症引起。尤其是,所述方法包括向个体施用治疗有效量的组合物,以有益于患有由疾病或创伤引起的眼损伤的个体的视力或在人中预防这样的疾病。最特别地,眼疾病选自白内障、角膜混浊(浑浊化)、青光眼、葡萄膜炎、眼内新生血管性疾病,尤其是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞(CRVO)、角膜新生血管形成、视网膜新生血管形成或年龄相关性黄斑变性(AMD)、更特别是AMD,最特别是干性AMD。

[0102] 在本发明的某些实施方案中,所述组合物包含:以重量计10%至69%,优选以重量计40%至60%,更优选以重量计48%至55%的CETP调节剂。

[0103] 在本发明的某些实施方案中,所述组合物还包含:以重量计1%至10%,优选以重量计5%至10%,更优选以重量计4%至8%的超级崩解剂。

[0104] 在如本文所述的本发明的某些实施方案中,超级崩解剂是吸湿性聚合赋形剂。尤其是,作为超级崩解剂的所述吸湿性聚合赋形剂是交联羧甲基纤维素钠。

[0105] 在特定实施方案中,本发明提供组合物,其包含:

[0106] a)S-[2-([1-(2-乙基丁基)-环己基]-羰基)氨基)苯基]2-甲基硫代丙酸酯,

[0107] b)微粒化的交聚维酮,和

[0108] c)交联羧甲基纤维素钠;

[0109] 可用于预防、治疗眼疾病,延迟眼疾病进展,和/或减少眼疾病,所述眼疾病如白内

障、角膜混浊(浑浊化)、青光眼、葡萄膜炎、眼内新生血管性疾病,尤其是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞(CRVO)、角膜新生血管形成、视网膜新生血管形成或年龄相关性黄斑变性(AMD),更特别是AMD,最特别是干性AMD。

[0110] 在如本文所述的本发明的某些实施方案中,所述组合物包含以重量计10%至69%的S-[2-([1-(2-乙基丁基)-环己基]-羰基)氨基)苯基]2-甲基硫代丙酸酯或其前药化合物。

[0111] 在本发明的某些实施方案中,所述药物组合物包含:以重量计10%至69%,优选以重量计40%至60%,更优选以重量计48%至55%的S-[2-([1-(2-乙基丁基)-环己基]-羰基)氨基)苯基]2-甲基硫代丙酸酯或其前药化合物。

[0112] 在如本文所述的本发明的某些实施方案中,所述组合物包含以重量计1%至10%,优选以重量计5%至10%,更优选以重量计5%至8%的交联羧甲基纤维素钠。更特别地,在某些实施方案中,所述组合物包含以重量计5%至7%的交联羧甲基纤维素钠。

[0113] 在特定实施方案中,所述组合物包含:

[0114] -以重量计10%至69%,优选以重量计40%至60%,更优选以重量计48%至55%的S-[2-([1-(2-乙基丁基)-环己基]-羰基)氨基)苯基]2-甲基硫代丙酸酯;

[0115] -以重量计1%至10%,优选以重量计5%至10%,更优选以重量计4%至8%的交联羧甲基纤维素钠,和

[0116] -以重量计30%至90%,优选以重量计34%至44%,更优选以重量计40%至44%的吸湿性聚合赋形剂;

[0117] 其中所述吸湿性聚合赋形剂选自羟丙基甲基纤维素、微晶纤维素和微粒化的交联的聚乙烯吡咯烷酮。

[0118] 在如本文所述的本发明的某些实施方案中,所述组合物包含:

[0119] a)以重量计48%至55%的S-[2-([1-(2-乙基丁基)-环己基]-羰基)氨基)苯基]2-甲基硫代丙酸酯;

[0120] b)以重量计4%至8%的交联羧甲基纤维素钠

[0121] c)以重量计32%至41%的不溶于水的吸湿性聚合物;和

[0122] d)以重量计4%至5%的可溶于水的吸湿性聚合物。

[0123] 在如本文所述的本发明的某些实施方案中,其中所述吸湿性聚合赋形剂选自羟丙基甲基纤维素、羟丙基纤维素、低取代羟丙基纤维素、羟乙基甲基纤维素、羧基聚亚甲基、甲基纤维素、乙基纤维素、羟乙基纤维素、醋酸纤维素、聚乙烯吡咯烷酮、交联聚乙烯吡咯烷酮、微粒化的交联聚乙烯吡咯烷酮、羧甲基纤维素钙、交联羧甲基纤维素、微晶纤维素、硅化的微晶纤维素、纤维素粉末、羧甲基淀粉、淀粉和预凝胶化的淀粉。

[0124] 在如本文所述的本发明的某些实施方案中,其中所述吸湿性聚合赋形剂是羟丙基甲基纤维素、微晶纤维素和微粒化的交联聚乙烯吡咯烷酮。

[0125] 所述药物组合物可以通过任何合适的方法,如药学领域公知的方法,例如,如Gennaro等人,Remington's Pharmaceutical Sciences(第18版,Mack Publishing Co., 1990),特别是第8部分:药物制剂和其制造中所述的那些的方法制备。所述方法包括将CETP

调节剂与药物组合物的其他组分联合的步骤。尤其是,本发明的组合物可以根据导致保持API基本上为晶体形式(疏水的、无定形API的量以重量计不超过10%)的任何已知方法制备。此外,本发明的组合物可以根据导致保持API基本上为晶体形式(具有蜡质平滑度的基本上无定形的疏水、不溶于水的化合物的量以重量计不超过10%)的任何已知方法制备。组合物,尤其是药物组合物可以根据W02004/082593和W02012/059447制备。

[0126] 在如本文所述的本发明的某些实施方案中,两种稀释剂是吸湿性聚合赋形剂。尤其是,作为稀释剂的吸湿性聚合赋形剂是乙基纤维素、微粒化的交联聚乙烯吡咯烷酮、微晶纤维素、硅化的微晶纤维素、纤维素粉末、淀粉、预凝胶化的淀粉。

[0127] 在如本文所述的本发明的某些实施方案中,存在至少两种吸湿性聚合赋形剂。

[0128] 在如本文所述的本发明的某些实施方案中,超级崩解剂和至少一种稀释剂,或至少两种稀释剂是吸湿性聚合赋形剂。更优选地,至少超级崩解剂和一种稀释剂是吸湿性聚合赋形剂。

[0129] 在如本文所述的本发明的某些实施方案中,超级崩解剂和两种稀释剂是吸湿性聚合赋形剂。

[0130] 在如本文所述的本发明的某些实施方案中,存在以重量计至少30%的吸湿性聚合赋形剂,优选以重量计44%至50%。

[0131] 在本发明的某些实施方案中,超级崩解剂是交联羧甲基纤维素钠。尤其是,本发明包括以重量计多至6%的交联羧甲基纤维素钠。

[0132] 本发明提供物理上稳定的药物组合物,其包含以优选以重量计40%以上/单位的量嵌入由至少一种吸湿性聚合物组成的化学保护性吸湿性聚合物基质片剂的至少一种疏水的和水不稳定的胆固醇酯转移蛋白(CETP)调节剂或其组合,所述吸湿性聚合物例如羟丙基甲基纤维素(HPMC)、羟丙基纤维素(HPC)、低取代羟丙基纤维素(L-HPC)、羟乙基甲基纤维素(HEMC)、羧基亚甲基(卡波姆(Carbomer))、甲基纤维素(MC)、乙基纤维素(EC)、羟乙基纤维素(HEC)、醋酸纤维素、聚乙烯吡咯烷酮(PVP)、交联聚乙烯吡咯烷酮(交聚维酮)、微粒化的交联聚乙烯吡咯烷酮(微粒化的交聚维酮)、羧甲基纤维素钠(交联羧甲基纤维素钠、CMC Na)、羧甲基纤维素钙(交联羧甲基纤维素钙、CMC Ca)、交联羧甲基纤维素(交联CMC)、微晶纤维素(MCC)、硅化的微晶纤维素(硅化的MCC)、纤维素粉末、羧甲基淀粉(淀粉羟乙酸钠)、淀粉(玉米淀粉、马铃薯淀粉、水稻(rize)淀粉、小麦淀粉、木薯淀粉)、预凝胶化的淀粉或其组合。

[0133] 根据本发明,组合物至少包含以优选以重量计40%以上/单位的量嵌入由至少一种吸湿性聚合物组成的化学保护性吸湿性聚合物基质片剂的S-[2-([1-(2-乙基丁基)-环己基]-羰基)氨基)苯基]2-甲基硫代丙酸酯或其前药化合物或其组合,所述吸湿性聚合物例如羟丙基甲基纤维素(HPMC)、羟丙基纤维素(HPC)、低取代羟丙基纤维素(L-HPC)、羟乙基甲基纤维素(HEMC)、羧基亚甲基(卡波姆)、甲基纤维素(MC)、乙基纤维素(EC)、羟乙基纤维素(HEC)、醋酸纤维素、聚乙烯吡咯烷酮(PVP)、交联聚乙烯吡咯烷酮(交聚维酮)、微粒化的交联聚乙烯吡咯烷酮(微粒化的交聚维酮)、羧甲基纤维素钠(交联羧甲基纤维素钠、CMC Na)、羧甲基纤维素钙(交联羧甲基纤维素钙、CMC Ca)、交联羧甲基纤维素(交联CMC)、微晶纤维素(MCC)、硅化的微晶纤维素(硅化的MCC)、纤维素粉末、羧甲基淀粉(淀粉羟乙酸钠)、淀粉(玉米淀粉、马铃薯淀粉、水稻(rize)淀粉、小麦淀粉、木薯淀粉)、预凝胶化的淀粉或其

组合。

[0134] 尤其是根据本发明,所述组合物包含嵌入由羟丙基甲基纤维素、羧甲基纤维素钠、微晶纤维素和微粒化的交联聚乙烯吡咯烷酮组成的化学保护性吸湿性聚合物基质片剂中的至少一种疏水的和水不稳定的胆固醇酯转移蛋白(CETP)调节剂。

[0135] 尤其是根据本发明,所述组合物至少包含嵌入由羟丙基甲基纤维素、羧甲基纤维素钠、微晶纤维素和微粒化的交联聚乙烯吡咯烷酮组成的化学保护性吸湿性聚合物基质片剂中的S-[2-([1-(2-乙基丁基)-环己基]-羰基)氨基)苯基]2-甲基硫代丙酸酯。

[0136] 在特定的实施方案中,所述组合物至少包含以优选以重量计40%以上/单位的量嵌入由羟丙基甲基纤维素、羧甲基纤维素钠、微晶纤维素和微粒化的交联聚乙烯吡咯烷酮组成的化学保护性吸湿性聚合物基质片剂中的S-[2-([1-(2-乙基丁基)-环己基]-羰基)氨基)苯基]2-甲基硫代丙酸酯。

[0137] 在本发明的另一实施方案中,提供组合物,其包含:

[0138] a)以重量计48%至55%的S-[2-([1-(2-乙基丁基)-环己基]-羰基)氨基)苯基]2-甲基硫代丙酸酯;

[0139] b)以重量计小于12%的微粒化的交聚维酮;和

[0140] c)以重量计35%至44%的羟丙基甲基纤维素、微晶纤维素和交联羧甲基纤维素钠。

[0141] 在本发明的另一实施方案中,提供组合物,其包含:

[0142] a)S-[2-([1-(2-乙基丁基)-环己基]-羰基)氨基)苯基]2-甲基硫代丙酸酯;

[0143] b)微晶纤维素;

[0144] c)微粒化的交聚维酮;

[0145] d)羟丙基甲基纤维素;和

[0146] e)交联羧甲基纤维素钠。

[0147] 在本发明的另一实施方案中,提供组合物,其包含:

[0148] a)以重量计48%至55%的S-[2-([1-(2-乙基丁基)-环己基]-羰基)氨基)苯基]2-乙基硫代丙酸酯;

[0149] b)以重量计24%至26%的微晶纤维素;

[0150] c)以重量计11%至12%的微粒化的交聚维酮;

[0151] d)以重量计4%至5%的羟丙基甲基纤维素;

[0152] e)以重量计4%至6%的交联羧甲基纤维素钠。

[0153] 在本发明的另一实施方案中,提供组合物,其包含:

[0154] a)以重量计48%至55%的S-[2-([1-(2-乙基丁基)-环己基]-羰基)氨基)苯基]2-乙基硫代丙酸酯;

[0155] b)以重量计24%至26%的微晶纤维素;

[0156] c)以重量计11%至12%的微粒化的交聚维酮;

[0157] d)以重量计4%至5%的羟丙基甲基纤维素;

[0158] e)以重量计4%至6%的交联羧甲基纤维素钠;

[0159] f)以重量计0至1%的硬脂酸镁;

[0160] g)以重量计0至1%的胶体二氧化硅;

[0161] h)以重量计0至1%的硬脂酰富马酸钠。

[0162] 在本发明的特定实施方案中,本文所述的组合物是药物组合物。

[0163] 所述药物组合物可以是,例如,丸剂、胶囊或片剂的形式(各自含有预定量的CETP调节剂,并且尤其是包衣的以容易吞咽),粉末或颗粒的形式。尤其是,所述药物组合物是片剂形式,其包含CETP调节剂和其中使用和描述的片剂的组分。为了口服施用,细粉或颗粒可以含有稀释剂、分散剂和/或表面活性剂并且可以以干燥状态存在于,例如,胶囊或锭剂中,或存在于片剂中,其中可以包括粘合剂和润滑剂。组分如甜味剂、芳香剂、防腐剂、悬浮剂、增稠剂、和/或乳化剂也可以存在于药物组合物中。

[0164] 在特定实施方案中,本文中的组合物是用聚乙烯醇系包衣(PVA-系包衣),特别是用20mg以下PVA-系包衣,更特别是15mg PVA-系包衣膜包衣的。

[0165] 在本发明的某些实施方案中,所述组合物包含100mg至600mg的S-[2-([1-(2-乙基丁基)-环己基]-羰基]氨基)苯基]2-甲基硫代丙酸酯。尤其是,所述组合物包含150mg至450mg的S-[2-([1-(2-乙基丁基)-环己基]-羰基]氨基)苯基]2-甲基硫代丙酸酯。更特别地,所述组合物包含250mg至350mg的S-[2-([1-(2-乙基丁基)-环己基]-羰基]氨基)苯基]2-甲基硫代丙酸酯。最特别地,所述组合物包含250mg至350mg的S-[2-([1-(2-乙基丁基)-环己基]-羰基]氨基)苯基]2-甲基硫代丙酸酯。

[0166] 在另一实施方案中,用于儿科使用,所述组合物包含25mg至300mg的S-[2-([1-(2-乙基丁基)-环己基]-羰基]氨基)苯基]2-甲基硫代丙酸酯。尤其是儿科组合物包含75mg至150mg的S-[2-([1-(2-乙基丁基)-环己基]-羰基]氨基)苯基]2-甲基硫代丙酸酯。

[0167] 为了有效,CETP调节剂必须被吸收入血液。优选口服剂量给药CETP调节剂,因为为了有效,必须有规律地,如每日服用所述“CETP调节剂”。

[0168] CETP调节剂可以以任何合适的剂量施用给哺乳动物(例如,以实现治疗有效量)。例如,用于施用给患者的合适剂量的治疗有效量的式I的化合物将在大约100mg至约1800mg/天。尤其是,所需剂量为大约300mg至约900mg/天。优选剂量是约600mg/天。

[0169] 在另一实施方案中,本发明提供试剂盒,其包含如本文所述的CETP调节剂,黄体素以及任选地与玉米黄质的一种或多种立体异构体一起。在更特别的实施方案中,本发明提供试剂盒,其包含如本文所述的CETP调节剂,黄体素以及任选地与玉米黄质的一种或多种立体异构体一起,处方信息(也称为“说明书”),泡罩包装或瓶(HDPE或玻璃)和容器。处方信息优选包括关于施用CETP调节剂(例如式(I)的化合物与食物一起),特别是改善CETP调节剂的生物利用度,对患者的建议。

[0170] 在另一实施方案中,本发明提供试剂盒,其包含如本文所述的组合物,黄体素以及任选地与玉米黄素的一种或多种立体异构体一起。在更特别的实施方案中,本发明提供试剂盒,其包含如本文所述的组合物,黄体素以及任选地与玉米黄素的一种或多种立体异构体一起,处方信息(也称为“说明书”),泡罩包装或瓶(HDPE或玻璃)和容器。处方信息优选包括关于施用CETP调节剂(例如式(I)的化合物与食物一起),特别是改善CETP调节剂的生物利用度,对患者的建议。

[0171] 在另一实施方案中,本发明提供试剂盒,其含有包含治疗有效量的S-[2-([1-(2-乙基丁基)-环己基]-羰基]氨基)苯基]2-甲基硫代丙酸酯和以组合物重量计至少30重量%的吸湿性聚合赋形剂的组合物,黄体素以及任选地与玉米黄质的一种或多种立体异构体一

起,处方信息,泡罩包装或瓶和容器。本发明的特别实施方案提供如本文所述的试剂盒,其中处方信息包括对患者的关于与食物一起施用S-[2-([1-(2-乙基丁基)-环己基]-羰基]氨基)苯基]2-甲基硫代丙酸酯的建议。

[0172] 在另一实施方案中,本发明提供片剂,其包含如本文所述的组合物。

[0173] 在另一实施方案中,本发明提供如本文所述的组合物,其用于制备药物,所述药物用于治疗或预防眼疾病,如白内障、角膜混浊(浑浊化)、青光眼、葡萄膜炎、眼内新生血管性疾病,尤其是增生性视网膜病变、脉络膜新生血管形成(CNV)、糖尿病性及其他缺血相关视网膜病变、糖尿病性黄斑水肿、病理性近视、脑视网膜血管瘤病、眼组织胞浆菌病、视网膜中央静脉阻塞(CRVO)、角膜新生血管形成、视网膜新生血管形成或年龄相关性黄斑变性(AMD),更特别是AMD,最特别是干性AMD,尤其是其中S-[2-([1-(2-乙基丁基)-环己基]-羰基]氨基)苯基]2-甲基硫代丙酸酯以100mg至1800mg,特别是300mg至900mg,更特别是600mg的每日剂量施用,更特别是其中S-[2-([1-(2-乙基丁基)-环己基]-羰基]氨基)苯基]2-甲基硫代丙酸酯与食物一起施用。

[0174] 从以下实施例,本发明的其他特征和实施方案将变得显而易见,给出所述实施例以说明本发明而不是限制其预期的范围。

[0175] 实施例A:

[0176] 利用STOE STADI P衍射仪(Cu K α 辐射源,初级单色器,位置灵敏探测器,角度范围3°至42° 2 θ ,大约60分钟总测量时间),在环境条件以透射几何结构(transmission geometry)记录S-[2-([1-(2-乙基丁基)-环己基]-羰基]氨基)苯基]2-甲基硫代丙酸酯晶形A的XRPD图。制备样品并且在不进一步加工(例如研磨或过筛)所述物质的情况下分析。

[0177]

2 θ /°	相对强度/%
7.9	86.3
8.5	16.2
11.7	30.7
12.7	17.1
17.1	41.6
18	14.6
18.5	100
20.2	27.2
22.1	33.7
24.7	11.9

[0178] 实施例1:叙利亚仓鼠研究a:

[0179] 材料和方法

[0180] 为仓鼠(7周龄)喂食含有4.5%脂肪和0.05%胆固醇和椰油(70g/kg干燥食物)的标准啮齿类动物饲料14天。喂食两周后,将仓鼠分配到10只动物的两个实验组并且给予补充有0.1%(w:w)FLORAGLO(黄体素5.2%,玉米黄质0.5%,DSM营养产品)的与之前相同的饲料:组1不接受治疗,组2给予作为0.375%的食品掺和料(~400mg/kg)的达塞曲匹。

[0181] 14天的治疗和4小时的禁食后,收集血浆、肝和眼并保持冷冻,直到分析。通过

HPLC-MS,使用隐黄素作为内标确定来自2只仓鼠的血浆、肝和汇集的视杯(eyecups)中的黄体素和玉米黄质水平。在BHT的存在下在暗环境中用己烷/乙酸乙酯直接萃取血浆样品。将肝样品和汇集的视杯(n=4)首先在BHT的存在下,使用合适的溶剂,在Precellys组织匀浆器中匀浆,然后皂化,之后用己烷/乙酸乙酯萃取。将有机相用水洗涤。将所有有机相干燥并恢复在含有0.1%的甲醇中。在偶联于ACCLAIM C30RP柱(Thermo Fisher Scientific, Reinach)的Acquity I-型UPLC(Waters AG, Baden-Dättwil)的APCI模式的Waters TQ-S上完成HPLC-MS。

[0182] 结果

[0183] 达塞曲匹治疗后血浆、肝和视杯的改变。

		黄体素	玉米黄质
[0184]	血浆	+ 55.7	+ 164
	<i>p</i>	**	***
	肝	+ 107	+ 222.9
	<i>p</i>	***	***
	Eyecups	+ 164.6	+ 114
	<i>p</i>	***	***

[0185] 以相对于对照的%计;Wilcoxon/Kruskal-Wallis测试

[0186] * $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

[0187] 达塞曲匹以+55.7% $p < 0.0019$,+107% $p < 0.0002$ 和+165% $p < 0.0009$ 显著增加血浆、肝和视杯黄体素水平,并且以+164% $p < 0.0002$,+222.9% $p < 0.0002$ 和+114% $p < 0.0088$ 显著增加玉米黄质水平。

[0188] 实施例2:叙利亚仓鼠研究b:

[0189] 材料和方法

[0190] 为仓鼠(7周龄)喂食含有4.5%脂肪和0.05%胆固醇和椰油(70g/kg干燥食物)的标准啮齿动物饲料达14天。2周的高脂肪饲料喂养后,将仓鼠分为10只动物的3个实验治疗组,其各自基于血脂水平,并且提供补充以0.1%(w/w)FLORAGLO(与研究2相同的组合物)的与之前相同的饲料,并且(分为)没有治疗(组1),0.320%的达塞曲匹(w:w,~300mg/kg,组2),或0.024%的安塞曲匹(w:w,~25mg/kg,组3)。

[0191] 14天的治疗后,收集血浆和肝用于如研究a中所述的黄体素和玉米黄质分析。

[0192] 结果

[0193] 达塞曲匹和安塞曲匹治疗后血浆和肝的变化。

		达塞曲匹		安塞曲匹	
		黄体素	玉米黄质	黄体素	玉米黄质
[0194]	血浆	+ 95	+ 101	ns	ns
	<i>p</i>	***	***		
	肝	+ 90	+ 109	-32	-31
	<i>p</i>	**	***	*	*

[0195] 以相对于对照的%计;Wilcoxon/Kruskal-Wallis测试

- [0196] * $p<0.05$; **: $p<0.01$; ***: $p<0.001$
- [0197] 可以从两个体内研究得出结论:达塞曲匹治疗增加了保护性抗氧化剂膳食叶黄素如黄体素和玉米黄质的肠摄取和组织分布。
- [0198] 测量的其他变量。

	达塞曲匹	安塞曲匹
[0199] 总胆固醇	ns	+28 **
HDL-C	ns	+54 ***
VLDL-C	-27 *	ns
LDL-C	ns	-99 ***
甘油三酯	-37 **	ns

- [0200] 以相对于对照的%计;Wilcoxon/Kruskal-Wallis测试
- [0201] *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$ 。

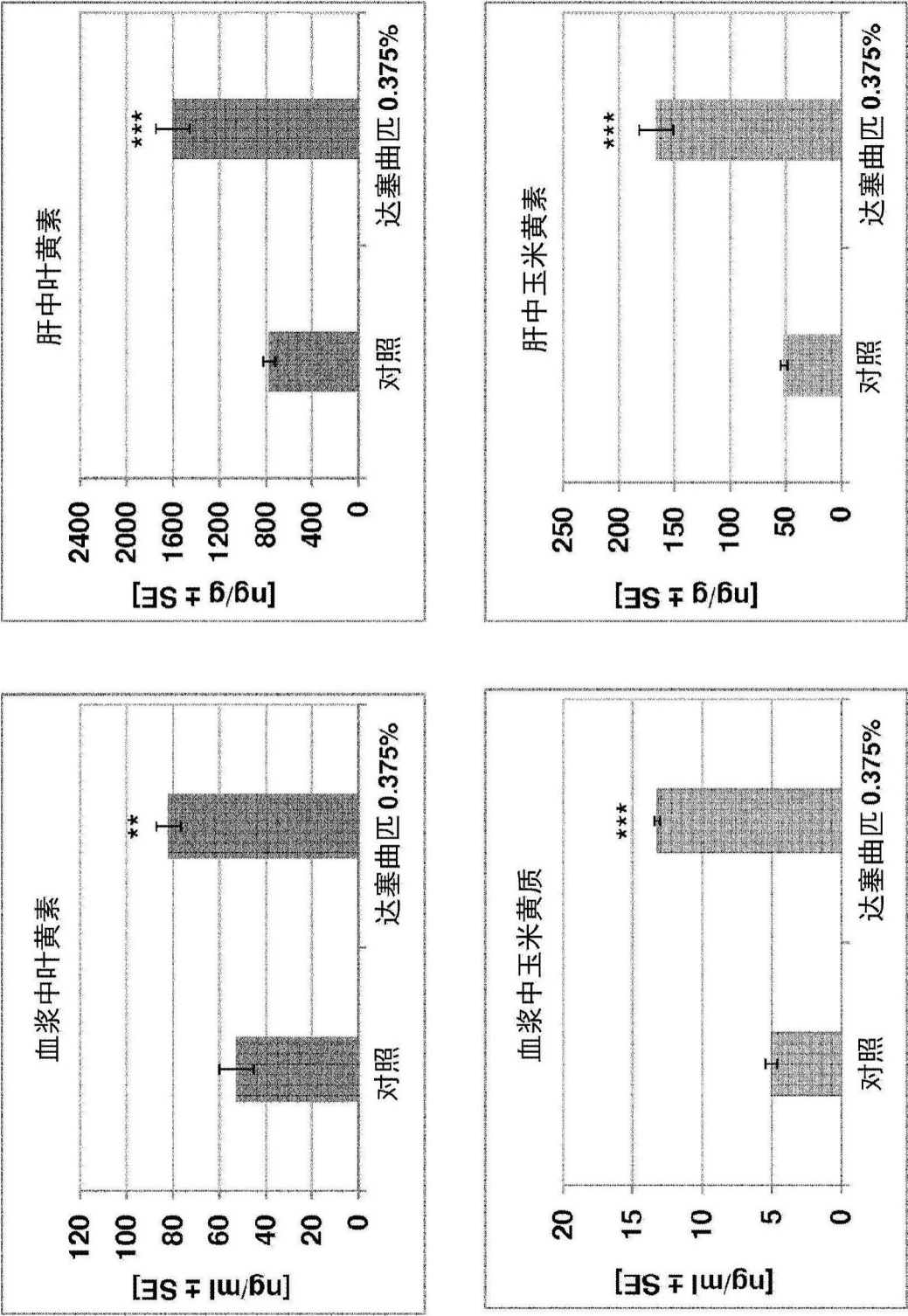


图1

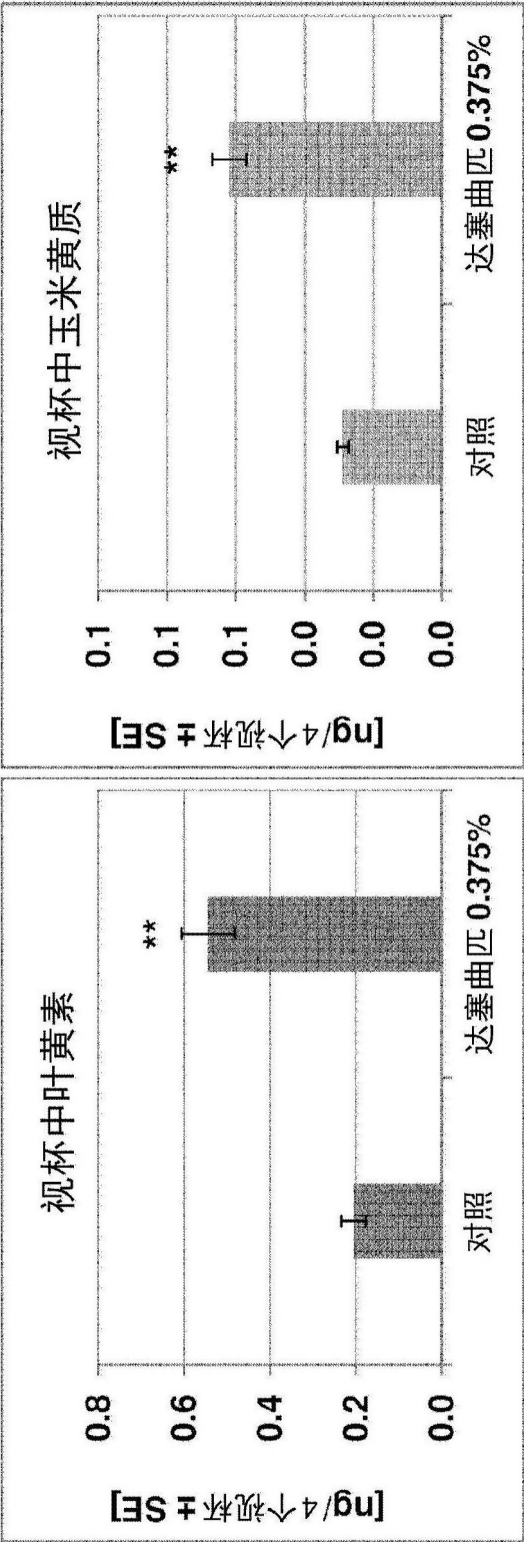


图2

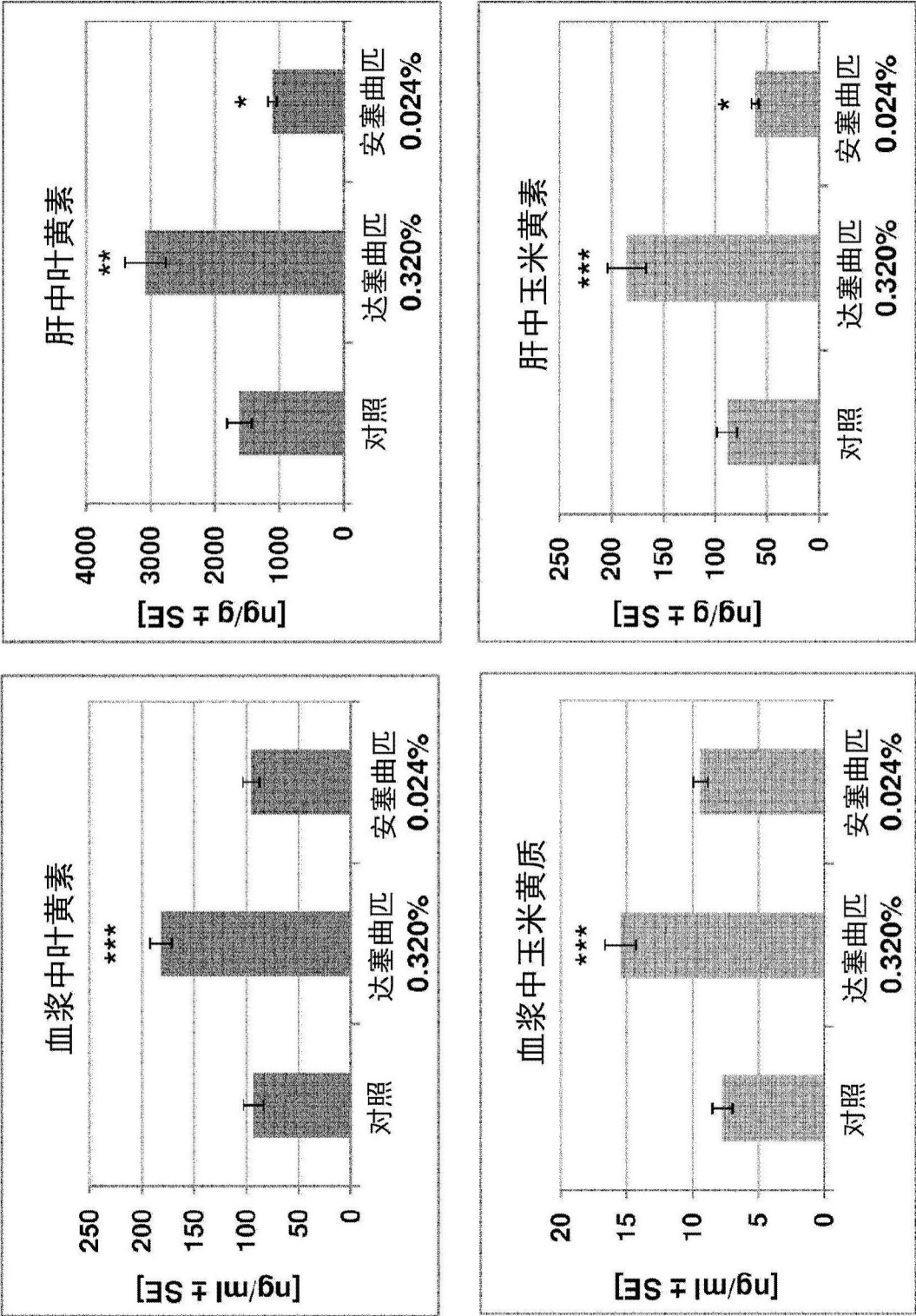


图3