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(54) Title: PHARMACEUTICAL COMBINATIONS COMPRISING A DGAT1 INHIBTOR AND A TRIGLYCERIDE LOWERING DRUG

(57) Abstract: The present invention relates to a pharmaceutical combination, such as a combined preparation or pharmaceutical composition, respectively, comprising at least one DGAT1 inhibitor, or a pharmaceutically acceptable salt or ester thereof, at least one kind of triglyceride lowering drug selected from the group consisting of (a) at least one PPAR alpha agonist or a pharmaceutically acceptable salt thereof or ester thereof, and (b) at least one compound selected from the group consisting of (i) natural or synthetic omega-3 fatty acids or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof, or (ii) omega-3 oils, and optionally at least one pharmaceutically acceptable carrier for simultaneous, separate or sequential use, in particular for the treatment of hypertriglyceridemia, in particular chylomicronemia (also called hyperchylomicronemia); a pharmaceutical composition comprising such a combination; the use of such a combination for the preparation of a medicament for the treatment of hypertriglyceridemia, in particular chylomicronemia (also called hyperchylomicronemia; a commercial package or product comprising such a combination as a combined preparation for simultaneous, separate or sequential use; and to a method of treatment of a warm-blooded animal, especially a human.

PHARMACEUTICAL COMBINATIONS COMPRISING A DGAT1 INHIBTOR AND A TRIGLYCERIDE LOWERING DRUG

BACKGROUND OF THE INVENTION

The present invention relates to a pharmaceutical combination, such as a combined preparation or pharmaceutical composition, respectively, comprising at least one DGAT1 inhibitor, or a pharmaceutically acceptable salt or ester thereof,

at least one kind of triglyceride lowering drug selected from the group consisting of

(a) at least one PPAR alpha agonist or a pharmaceutically acceptable salt thereof or ester thereof, and

(b) at least one compound selected from the group consisting of

(i) natural or synthetic omega-3 fatty acids or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof, or

(ii) omega-3 oils,

and optionally at least one pharmaceutically acceptable carrier for simultaneous, separate or sequential use, in particular for the treatment of hypertriglyceridemia, in particular chylomicronemia (also called hyperchylomicronemia); a pharmaceutical composition comprising such a combination; the use of such a combination for the preparation of a medicament for the treatment of hypertriglyceridemia, in particular chylomicronemia (also called hyperchylomicronemia; a commercial package or product comprising such a combination as a combined preparation for simultaneous, separate or sequential use; and to a method of treatment of a warm-blooded animal, especially a human.

Hyperlipidemia, or the presence of elevated levels of lipids in the bloodstream, can take the form of hypercholesterolemia (elevated cholesterol), hypertriglyceridemia (elevated triglyceride) or a combination of the two. Hypercholesterolemia, which can further be subdivided, is typically associated with increased risk of atherosclerosis cardiovascular disease. Hypertriglyceridemia occurs when the body's production or intake of triglyceride exceeds the body's ability to metabolize or remove the triglyceride from the bloodstream. The most severe form of hypertriglyceridemia is chylomicronemia (also called hyperchylomicronemia), and is associated with an increased risk of pancreatitis. Chylomicrons are lipoprotein particles that carry absorbed dietary fat from the gut to other body tissues via the bloodstream, and are typically present only during meal times. Chylomicronemia is defined as having the presence of chylomicrons in the bloodstream during times of fasting, and is typically associated with total plasma triglyceride levels above 1000 mg/dL.

The chylomicronemia syndrome refers to a set of clinical complications associated with high chylomicron levels. Typically, patients with the chylomicronemia syndrome have markedly elevated fasting triglyceride levels (1000-2000 mg/dL) with profound excursions (up to 5000 mg/dL and higher) following oral fat intake. The massively elevated plasma triglyceride levels are associated with a number of clinical findings and complications including recurrent episodes of pancreatitis, deposition of triglycerides in the skin in the form of eruptive xanthomas, hepatosplenomegaly, a milky pink appearance of the blood vessels in the back of the eye (lipemia retinalis), and mild neuro-cognitive deficits.

The chylomicronemia syndrome can be further subdivided into two groups based on ultracentrifugation of lipoprotein species (see "A system for phenotyping hyperlipoproteinemia", Fredrickson D.S., Lees R.S. Circulation, 1965 Mar; 31, pp. 321-327). Fredrickson classification Type I, also known as the familial chylomicronemia syndrome (FCS), patients have accumulation of only chylomicrons in the bloodstream whereas Fredrickson classification Type V, also known as Type V hyperlipoproteinemia, patients have accumulation of both chylomicrons and very low density lipoproteins (VLDL) in the bloodstream.

The familial chylomicronemia syndrome (FCS or Type I hyperlipoproteinemia) is caused by a homozygous or compound heterozygous defect in the clearance of chylomicrons from the bloodstream. The most common cause of FCS is a defect in lipoprotein lipase (LPL), the protein that hydrolyzes triglycerides carried on chylomicrons. Other causes of FCS include defects in apolipoprotein CII (apoCII, a co-activator of LPL) or glycosylphosphatidylinositol-anchored high-density lipoprotein–binding protein 1 (GPIHBP1, an anchoring protein of LPL).

Type I patients are usually identified by early onset as youth of hypertriglyceridemia and pancreatitis. Thus, patients with FCS typically present in childhood with massively elevated triglyceride levels (>2,000 mg/dL), and recurrent bouts of abdominal pain due to pancreatitis. Into adulthood, the triglyceride levels remain elevated, and patients typically experience multiple episodes of abdominal pain and pancreatitis, which can result in hospitalization and death. Patients also experience other manifestations including eruptive xanthomas, lipemia retinalis, hepatosplenomegaly, and mild neuro-cognitive deficits. The main therapeutic goal in FCS treatment is to prevent or treat pancreatitis via the reduction of triglycerides.

Unfortunately, standard lipid-lowering therapies, such as fibrates, omega-3 fatty acids, statins, and nicotinic acid derivatives (niacin), are not effective in lowering triglycerides in patients with FCS. Therefore, the standard of care therapy for FCS patients is a very low fat

diet (≤ 10% by calories), something which is very difficult to stay compliant with throughout a lifetime [The Familial Chylomicronemia Syndrome. Santamarina-Fojo 1998 Lipid Disorders, 27(3): 551-567].

Another approach to treat FCS that is under investigation is gene therapy using a replication-deficient Adeno-Associated Viral vector to deliver a naturally-occurring, 'beneficial' variant of LPL (Glybera®) intramuscularly. However this treatment is only transiently effective and requires immunosuppression with mycophenolate, cyclosporine, and steroids [Alipogene tiparvovec, and adeno-associated virus encoding the Ser(447)X variant of human lipoprotein lipase gene for the treatment of patients with lipoprotein lipase deficiency. Burnett JR., Hooper AJ. 2009 Curr Opin Mol Ther, 6, p. 681-691].

At present there is thus no effective pharmacotherapy for treating FCS and there is thus a need for new methods of treating familial chylomicronemia syndrome (FCS), also known as Type I hyperlipoproteinemia.

Type V hyperlipoproteinemia patients represent a second group at risk for the chylomicronemia syndrome and are usually diagosed by severe hypertriglyceridemia as adults. This is a heterogenous group at the extreme end of a spectrum of multifactorial hypertriglyceridemia. Patients with Type V hyperlipoproteinemia generally have both an underlying genetic cause and one or more acquired causes of hypertriglyceridemia. The underlying genetic causes include well characterized dyslipidemia such as familial combined hyperlipidemia (Type IIA), dysbetalipoproteinemia (Type III) and familial hypertriglyceridemia (Type VI), and a group of less well characterized dyslipidemias (e.g. heterozygous LPL deficiency, defects in apoA & apoC genes, defects in fatty acid binding and transport proteins). Acquired causes of hypertriglyceridemia include comorbid diseases (e.g. type 2 diabetes, obesity, insulin resistance, lipodystrophy, hypothyroidism), medications (e.g. beta blockers, thiazide diuretics, estrogen, glucocorticoids, transplant medications), and other factors (e.g. pregnancy, alcohol intake).

The primary goal of therapy in Type V patients is to reduce the triglyceride levels, and therefore reduce the risk of pancreatitis. Most patients can be successfully treated by addressing the underlying acquired cause(s) of the elevated triglycerides, such as reducing the amount of dietary fat intake, treating uncontrolled co-morbid diseases such as T2DM (Type 2 diabetes mellitus), discontinuing offending medications, and initiating lipid lowering medications such as fibrates, omega-3 fatty acids, or nicotinic acid derivatives (niacin) [Chylomicronemia Syndrome. Chait A., Brunzell J. Adv Intern Med 1992. 37:249-73.].

Despite optimal therapy, some Type V patients continue to have elevated triglyceride levels. There is thus a need for new methods of treating Type V hyperlipoproteinemia.

Recently, as described in WO 2011/123401, which publication is hereby incorporated into the present application by reference, it has been found that DGAT1 inhibitors, or a pharmaceutically acceptable salt or ester thereof, reduce postprandial triglyceride levels to a clinically significant extent, in patients, especially patients with the chylomicronemia syndrome (including patients with familial chylomicronemia syndrome and patients with Type V hyperlipoproteinemia).

SUMMARY OF THE INVENTION

The present invention relates to the control of triglyceride levels in patients, in particular in patients with hyperlipoproteinemia type I (FCS) as well as the more resistant Type IV, V, and multifactorial cases (non-FCS) that often remain hypertriglyceridemic or at risk of chylomicronemia despite interventions. For these patients there are few alternatives and currently approved triglyceride lowering agents have not proven effective to sustainably reduce triglyceride values below the threshold of risk for pancreatitis associated with elevated fasting or post-prandial triglyceride levels.

Surprisingly, a pharmaceutical combination, such as a combined preparation or pharmaceutical composition, respectively, comprising

at least one DGAT1 inhibitor, or a pharmaceutically acceptable salt or ester thereof, and

at least one kind of triglyceride lowering drug selected from the group consisting of

(a) at least one PPAR alpha agonist or a pharmaceutically acceptable salt thereof or ester thereof, and

(b) at least one compound selected from the group consisting of

(i) natural or synthetic omega-3 fatty acids or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof, or

(ii) omega-3 oils,

and optionally at least one pharmaceutically acceptable carrier offers significant benefits in the treatment of hypertriglyceridemia, in particular chylomicronemia (also called hyperchylomicronemia).

The invention therefore provides a pharmaceutical combination, such as a combined preparation or pharmaceutical composition, respectively, separately or together, suitable for

the treatment of hypertriglyceridemia, in particular chylomicronemia (also called hyperchylomicronemia) comprising

at least one DGAT1 inhibitor, or a pharmaceutically acceptable salt or ester thereof, and

at least one kind of triglyceride lowering drug selected from the group consisting of

(a) at least one PPAR alpha agonist or a pharmaceutically acceptable salt thereof or ester thereof, and

(b) at least one compound selected from the group consisting of

(i) natural or synthetic omega-3 fatty acids or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof, or

(ii) omega-3 oils,

and optionally at least one pharmaceutically acceptable carrier.

The DGAT1 inhibitor is preferably selected from (4-{4-[5-(6-Trifluoromethyl-pyridin-3-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid, or a pharmaceutically acceptable salt or ester thereof, and (4-{4-[5-(Benzo[d]oxazol-2-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid or a pharmaceutically acceptable salt or ester thereof.

DETAILED DESCRIPTION OF THE INVENTION

DGAT1 Inhibitors

Diacylglycerol acyltransferase (DGAT) catalyzes the final step in triglyceride (TG) synthesis. The two isoforms of the enzyme in humans (DGAT1 and DGAT2) are highly expressed in TG synthesizing tissues such as the liver and adipocytes, and to a lesser degree in skeletal muscle and the gut wall. The two isoforms have different functions in mammals as shown in biochemical experiments and studies involving knockout mice. DGAT2 is essential for TG metabolism so that when TG content in newborn DGAT2-deficient mice is severely reduced (by approximately 90%), the mice lack substrates for oxidative metabolism. They also lack essential fatty acids, resulting in abnormalities in skin lipids and epidermal barrier function. As a result, newborn DGAT2-deficient mice rapidly become dehydrated and die within hours after birth (Stone et al 2004, J. Biol Chem, 279(12):11767-76). On the other hand, DGAT1 plays a modest role in TG metabolism in the gut wall by re-esterifying absorbed dietary lipid into TG. DGAT1-deficient mice are viable and have more modest reductions in tissue TG (Smith et al., 2000, Nat Genet, 25, 87-90). When given a high fat meal, DGAT1-deficient mice are resistant to the typical postprandial hypertriglyceridemia as a result of decreased chylomicron production.

DGAT1 inhibitors useful in the pharmaceutical combination, such as a combined preparation or pharmaceutical composition, respectively, of the present invention may be any DGAT1 inhibitor known in the art.

For example, the DGAT1 inhibitor may be chosen from those described in WO2007/126957 and in WO2009/040410. The DGAT1 inhibitor may be peptidal or non-peptidal in nature, however, the use of a non-peptidal DGAT1 inhibitor is preferred.

In one embodiment, the DGAT1 inhibitor useful in the pharmaceutical combination, such as a combined preparation or pharmaceutical composition, respectively, of the present invention is a compound which is selected from:
(4-{6-[5-(4-Chloro-phenyl)-[1,3,4]oxadiazol-2-yl]-1H-benzoimidazol-2-yl}-3,5-dimethyl-phenoxy)-acetic acid,
(3,5-Dichloro-4-{6-[5-(4-chloro-phenyl)-[1,3,4]oxadiazol-2-yl]-1H-benzoimidazol-2-yl}-phenoxy)-acetic acid,
3-(4-{6-[5-(4-Methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-1H-benzoimidazol-2-yl}-3,5-dimethyl-phenyl)-propionic acid,
3-(4-{6-[5-(3-Chlorophenylamino)-[1,3,4]oxadiazol-2-yl]-1H-benzoimidazol-2-yl}-3,5-dimethylphenyl)-propionic acid,
3-(4-{6-[5-(4-Methoxyphenylamino)-[1,3,4]oxadiazol-2-yl]-1H-benzimidazol-2-yl}-3,5-dimethylphenyl)-propionic acid,
3-(4-{6-[5-(4-Chloro-phenyl)-[1,3,4]oxadiazol-2-yl]-1H-benzoimidazol-2-yl}-3,5-dimethyl-phenyl)-propionic acid,
3-(4-{5-[5-(4-Methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-1H-benzoimidazol-2-yl}-3,5-dimethyl-phenyl)-2,2-dimethyl-propionic acid,
[3-(4-{6-[5-(4-Chloro-phenyl)-[1,3,4]oxadiazol-2-yl]-1H-benzoimidazol-2-yl}-3,5-dimethyl-phenyl)-propyl]-phosphonic acid,
(3-{3,5-Dimethyl-4-[6-(5-phenyl-[1,3,4]oxadiazol-2-yl)-1H-benzoimidazol-2-yl]-phenyl}-propyl)-phosphonic acid,
[3-(4-{6-[5-(4-Methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-1H-benzoimidazol-2-yl}-3,5-dimethyl-phenyl)-propyl]-phosphonic acid,
3-{4-[6-(5-Methoxy-[1,3,4]oxadiazol-2-yl)-1H-indol-2-yl]-3,5-dimethylphenyl}-propionic acid, and
3-(3,5-Dichloro-4-{6-[5-(4-chloro-phenyl)-[1,3,4]oxadiazol-2-yl]-1H-benzoimidazol-2-yl}-phenyl)-propionic acid,
or a pharmaceutically acceptable salt or ester therof.

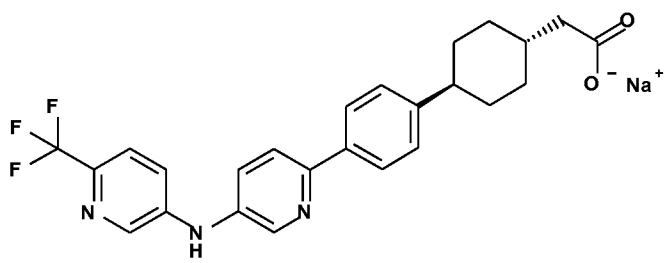
In another embodiment, the DGAT1 inhibitor is a compound which is selected from
(4-{6-[5-(4-Chloro-phenyl)-[1,3,4]oxadiazol-2-yl]-1H-benzoimidazol-2-yl}-3,5-dimethyl-phenoxy)-acetic acid,
3-(4-{6-[5-(4-Methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-1H-benzoimidazol-2-yl}-3,5-dimethyl-phenyl)-propionic acid,
3-(4-{6-[5-(4-methoxyphenylamino)-[1,3,4]oxadiazol-2-yl]-1H-benzimidazol-2-yl}-3,5-dimethylphenyl)-propionic acid,
3-(4-{5-[5-(4-Methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-1H-benzoimidazol-2-yl}-3,5-dimethyl-phenyl)-2,2-dimethyl-propionic acid and,
[3-(4-{6-[5-(4-Chloro-phenyl)-[1,3,4]oxadiazol-2-yl]-1H-benzoimidazol-2-yl}-3,5-dimethyl-phenyl)-propyl]-phosphonic acid;
or a pharmaceutically acceptable salt or ester thereof.

In one embodiment of the invention, the DGAT1 inhibitor is selected from
(4-{4-[5-(6-Trifluoromethyl-pyridin-3-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid, and
(4-{4-[5-(Benzo[d]oxazol-2-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid,
or a pharmaceutically acceptable salt or ester thereof.

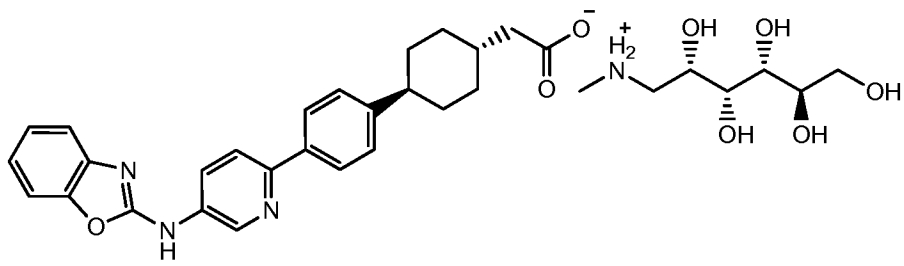
In a further embodiment, the above listed compounds are in the form of their corresponding potassium, sodium, hydrochloric, methanesulfonic, phosphoric or sulfuric acids salts.

The DGAT1 inhibitors according to the present invention and their salts can be prepared for example by the methods described in WO2007/126957 and in WO2009/040410, these methods being incorporated herein by reference.

In another embodiment of the invention the DGAT1 inhibitor is trans-(4-{4-[5-(6-Trifluoromethyl-pyridin-3-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid, or a pharmaceutically acceptable salt or ester thereof. In another embodiment, the DGAT1 inhibitor is trans-(4-{4-[5-(6-Trifluoromethyl-pyridin-3-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid, sodium salt. In particular, the DGAT-1 inhibitor is of the following formula:



In another embodiment of the invention the DGAT1 inhibitor is 2-((1R,4R)-4-(4-(5-(benzo[d]oxazol-2-ylamino)pyridin-2-yl)phenyl)cyclohexyl)acetic acid or a pharmaceutically acceptable salt or ester thereof. In another embodiment, the DGAT1 inhibitor is 2-((1R,4R)-4-(4-(5-(benzo[d]oxazol-2-ylamino)pyridin-2-yl)phenyl)cyclohexyl)acetic acid meglumine salt. In particular, the DGAT-1 inhibitor is of the following formula:



Prodrug derivatives of any compound of the invention are derivatives of said compounds which following administration release the parent compound *in vivo* via some chemical or physiological process, e.g., a prodrug on being brought to the physiological pH or through enzyme action is converted to the parent compound. Exemplary prodrug derivatives are, e.g., esters of free carboxylic acids and S-acyl and O-acyl derivatives of thiols, alcohols or phenols. Preferred are pharmaceutically acceptable ester derivatives convertible by solvolysis under physiological conditions to the parent carboxylic acid, e.g., lower alkyl esters, cycloalkyl esters, lower alkenyl esters, benzyl esters, mono- or di-substituted lower alkyl esters, such as the omega-(amino, mono- or di-lower alkylamino, carboxy, lower alkoxycarbonyl)-lower alkyl esters, the alpha-(lower alkanoyloxy, lower alkoxycarbonyl or di-lower alkylaminocarbonyl)-lower alkyl esters, such as the pivaloyloxymethyl ester and the like conventionally used in the art.

In view of the close relationship between the free compounds, the prodrug derivatives and the compounds in the form of their salts, whenever a compound is referred to in this context, a prodrug derivative and a corresponding salt is also intended, provided such is possible or appropriate under the circumstances.

The compounds, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization.

The activity of DGAT1 inhibitors according to the invention may for example be assessed by the methods well-described in the art, for example as disclosed in WO 2007/126957, in WO 2009/040410, page 48 to 49 of the published PCT application.

In general, the daily dose range of the DGAT1 inhibitor lies within the range of from about 0.0001 mg/kg to about 100 mg/kg, preferably from about 0.001 mg/kg to about 50 mg/kg body weight of a subject in single or divided doses. In one embodiment, the daily dose range of the DGAT1 inhibitor is from about 0.01 mg/kg to about 40 mg/kg, preferably from about 0.01 mg/kg to about 20 mg/kg body weight of a subject in single or divided doses. On the other hand, it may be necessary to use dosages outside these limits in some cases.

In the case where an oral composition is employed, a suitable dosage range is, e.g. from about 0.001 mg/kg to about 100 mg/kg of each compound in the composition per day, preferably from about 0.01 mg to about 2000 mg per day. For oral administration, the compositions are preferably provided in the form of tablets containing from 0.01 mg to 2,000 mg, e.g. 0.01, 0.05, 0.1, 0.2, 0.5, 1.0, 2.5, 5, 10, 15, 20, 25, 30, 40, 50, 75, 100, 125, 150, 175, 200, 225, 250, 500, 750, 850, 1,000 and 2,000 milligrams of each active ingredient for the symptomatic adjustment of the dosage to the subject to be treated. This dosage regimen may be adjusted to provide the optimal therapeutic response. For example, the DGAT1-inhibitor may be administered once daily over a period of several days or several (1, 2, 3, 4, or more) weeks. In another embodiment, the DGAT1-inhibitor is administered once, or several (e.g. 1, 2, 3) times daily.

The pharmaceutical combination, such as a combined preparation or pharmaceutical composition, respectively, of the present invention may comprise 0.1 to 1000 mg DGAT1 inhibitor, preferably 0.1 to 300 mg DGAT1 inhibitor, more preferably 1 to 100 mg DGAT1 inhibitor.

In one embodiment, the DGAT1 inhibitor is used at a dose of 1-150 mg, of 2-100 mg, of 2-50 mg, of 5-40 mg, of 10-40 mg, or of 20-40 mg. In another embodiment, the DGAT1 inhibitor is used at a dose of 5, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90 or 100 mg. In a preferred embodiment, the DGAT1 inhibitor is used at a dose of 5, 10, 20 or 40 mg. Thus in one embodiment, the DGAT1 inhibitor is used at a dose of at least 2, 5, 10, 15, 20 or 40 mg. In a related embodiment the DGAT1 inhibitor is used at a dose of 100 mg or less, such as 50 mg or less, 40 mg or less, 30 mg or less, 25 mg or less, or 15 mg or less. These doses are typically administered as the total dose per day.

In one embodiment, where the DGAT1 inhibitor is trans-4-[4-[5-[[6-(trifluoromethyl)-3-pyridinyl]amino]-2-pyridinyl]phenyl] cyclohexane acetic acid, or a pharmaceutically acceptable salt thereof, such as the sodium salt thereof, the DGAT1 inhibitor is used at a dose of 1-150 mg, of 2-100 mg, of 2-50 mg, of 5-40 mg, of 10-40 mg, or of 20-40 mg. In another embodiment, this DGAT1 inhibitor is used at a dose of 5, 10, 15, 20, 25, 30, 40 50, 60, 70, 80, 90 or 100 mg. In a preferred embodiment, this DGAT1 inhibitor is used at a dose of 5, 10, 20 or 40 mg. Thus in one embodiment, this DGAT1 inhibitor is used at a dose of at least 2, 5, 10, 15, 20 or 40 mg. In a related embodiment this DGAT1 inhibitor is used at a dose of 100 mg or less, such as 50 mg or less, 40 mg or less, 30 mg or less, 25 mg or less, or 15 mg or less. These doses are typically administered as the total dose per day. It is to be understood that the doses quoted herein refer to the DGAT1-inhibitor itself. When a pharmaceutically acceptable *salt* of the DGAT1-inhibitor is used, the doses used will need to be adjusted accordingly.

PPAR alpha agonists

The pharmaceutical combination, such as a combined preparation or pharmaceutical composition, respectively, of the present invention may comprise a PPAR alpha agonist.

Peroxisome proliferator-activated receptor (PPAR)-alpha is a ligand-activated transcriptional factor that belongs to the family of nuclear receptors. PPAR-alpha regulates the expression of genes involved in fatty acid beta-oxidation and is a major regulator of energy homeostasis.

PPAR-alpha is mainly expressed in tissues with elevated mitochondrial and peroxisomal fatty acid beta-oxidation rates, such as liver, heart muscle, kidney, skeletal muscle, and brown fat. PPAR-alpha is also present in cells of the arterial wall, in monocytes/macrophages, smooth muscle cells, and endothelial cells.

A "PPAR alpha agonist" is a compound or composition which when combined with PPAR alpha directly or indirectly (preferably binding directly to PPAR alpha) stimulates or increases an in vivo or in vitro reaction typical for the receptor, measured by assays known to one skilled in the art, for example as described in U.S. Patent 6,008,239 or Krey et al., "Fatty Acids, Eicosanoids, and Hypolipidemic Agents Identified as Ligands of Peroxisome Proliferator- Activated Receptors by Coactivator-Dependent Receptor Ligand Assay", Molecular Endocrinology, Vol. 11, pp. 779-791 (1997)).

"PPAR alpha agonists" are described to have many effects, including but not limited to increasing fatty acid oxidation rates, in particular peroxisomal and beta oxidation rates, reducing lipid levels (such as of cholesterol, LDL and VLDL), including reductions of plasma triglycerides, increasing HDLc, improving insulin sensitivity and inducing weight loss, and reducing hepatic lipids.

PPAR agonists can be identified by the following assays. Human PPAR-gamma 2, human PPAR-delta and human PPAR-alpha can be expressed as GST-fusion proteins in *E. coli*. Bacterial cells containing expression vectors encoding these fusion proteins can be propagated, expression of the proteins can be induced, and bacterial cells can be harvested by centrifugation. The pellet can be resuspended, cells disrupted in a French press and debris removed by centrifugation at 12, 000 X g. Recombinant human PPAR receptors can be further purified by affinity chromatography on glutathione sepharose. After application to the column, washing to remove non-specifically bound material, receptors can be eluted with glutathione. Glycerol (10 percent) can be added to stabilize the receptors and aliquots of the receptors can be stored at - 80 degrees centigrade.

For binding to PPAR-alpha, an aliquot of receptor can be incubated in TEGM (10 mM Tris, pH 7.2, 1 mM EDTA, 10 percent glycerol, 7 micro l 100 mL beta - mercaptoethanol, 10 mM Na molybdate, 1 mM dithiothreitol, 5 micro g/mL aprotinin, 2 micro g/mL leupeptin, 2 micro g/mL benzamidine and 0.5 mM PMSF) containing 0.1 percent non-fat dry milk and 5.0 nM [3H2]L-797773, (34 Ci/mmole), plus or minus test compound. (L-797733 is (3-(4-(3-phenyl-7 propyl-6-benz-[4,51- isoxazoloxy)butyloxy)) phenylacetic acid, Ex.62 in WO 97/28137). Assays can be incubated for about 16 hr at 4 degrees centigrade, in a final volume of 150 micro L. Unbound ligand can be removed by incubation with 100 micro L dextran/gelatin-coated charcoal, on ice, for about 10 min. After centrifugation at 3000 rpm for 10 min at 4°C, 50 microL of the supernatant fraction can be counted in a Topcount.

Pharmaceutically acceptable salt and esters of PPAR-alpha agonists are likewise included within the scope of this invention.

Compounds which are PPAR-alpha agonists include, but are not limited to, compounds such as those described in United States Patent No. 6,008,239, WO 97/27847, WO 97/27857, WO 97/28115, WO 97/28137, WO 97/28149, Hulin et al., Current Pharm. Design (1996) 2, pp. 85-102, and Willson et al. J. Med. Chem. 1996 vol. 39 pp. 665-669, all of which are hereby incorporated by reference.

A preferred PPAR alpha agonist according to the present invention is a fibrate. A fibrate or a fibric acid in general is an amphipathic carboxylic acid that has the ability to interact (agonize or antagonize) with nuclear transcription factors which influence lipid and lipoprotein synthesis and catabolism. In the present invention, fibrates include fibric acid derivatives and pharmaceutically acceptable salts and esters of such fibric acid derivatives.

Fibrates are known to lower the levels of triglyceride-rich lipoproteins, such as VLDL, to raise HDL levels, and to have variable effects on LDL levels. The effects on VLDL levels may result primarily from an increase in lipoprotein lipase activity, especially in muscle. This leads to enhanced hydrolysis of VLDL triglyceride content and enhanced VLDL catabolism. These compounds are also reported to decrease hepatic VLDL triglyceride synthesis, possibly by inhibiting fatty acid synthesis and by promoting fatty acid oxidation as a result of peroxisomal proliferation.

Fibrate compounds include, but are not limited to, fibric acid derivatives such as, for example, gemfibrozil (Lopid®), fenofibrate (TriCor®), micronized fenofibrate, fenofibric acid, bezafibrate (Bezalip®), clofibrate (Atromid-S®), ciprofibrate (Modalim®), and analogues, derivatives and pharmaceutically acceptable salts or ester thereof. Certain fibrate compounds as described in WO 92/10468 and WO 01/80852 are also incorporated by reference herein. These PPAR alpha compounds are disclosed in The Merck Index, 13' Edition, (2001), the contents of which is hereby incorporated by reference in its entirety as if set forth in full herein.

Fenofibrate or fenofibric acid, respectively, is commercially available for example under the brand names Tricor™ and Trilipix™. Fenofibric acid, the active metabolite of fenofibrate, lowers plasma triglycerides apparently by inhibiting triglyceride synthesis, resulting in a reduction of VLDL released into the circulation, and also by stimulating the catabolism of triglycerides rich lipoprotein (i.e. VLDL). The recommended daily dose of fenofibrate is of between 40 and 200 mg, such as 43 mg/day, 48 mg/day, 67 mg/day, 130 mg/day, 145 mg/day, 160 mg/day or 200 mg/day. The recommended daily dose of fenofibric acid, such as Trilipix™, is of between 45 mg/day and 135 mg/day.

Clofibrate is commercially available as Atromid-S™ capsules. Clofibrate lowers elevated serum lipids by reducing the very low-density lipoprotein fraction that is rich in triglycerides and thereby reduces serum cholesterol. Clofibrate may also inhibit the hepatic release of lipoproteins (particularly VLDL) and potentiate the action of lipoprotein lipase. The

recommended daily dose of clofibrate, such as Atromid-S™ is 2000 mg/day, administered in divided doses, such as 500 mg 4 times/day; some patients may respond to lower doses.

Gemfibrozil is commercially available as Lopid™ tablets. Gemfibrozil is a lipid regulating agent that decreases serum triglycerides and very low density lipoprotein cholesterol, and increases high density lipoprotein cholesterol. The recommended daily dose of gemfibrozil is 1200 mg, administered in two divided doses.

In one embodiment of the invention the fibrate is selected from the group consisting of clofribrate, gemfibrozil, fenofibrate, micronized fenofibrate, fenofibric acid, ciprofibrate and bezafibrate. In another embodiment of the invention the fibrate is fenofibrate. In still another embodiment of the invention the fibrate is fenofibrate or fenofibric acid.

In general, in the case of fibrates, the dose can range from about 20 mg/day to about 2500 mg/day, more particularly from about 40 mg/day to about 2000 mg/day in single or divided doses, or any other dose, depending upon the specific fibrate, as is normally employed in the art, for example, as indicated in the Physician's Desk Reference and The Merck Index (Twelfth Edition), the contents of both of which are incorporated herein by reference.

Natural or synthetic omega-3 fatty acids or omega-3 oils

The pharmaceutical combination, such as a combined preparation or pharmaceutical composition, respectively, of the present invention may comprise natural or synthetic omega-3 fatty acids or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts or mixtures thereof or omega-3 oils.

Omega-3 fatty acids have been found to have beneficial effects on the risk factors for cardiovascular diseases, especially mild hypertension, hypertriglyceridemia and on the coagulation factor VII phospholipid complex activity. Omega-3 fatty acids lower serum triglycerides, increase serum HDL- cholesterol, lower systolic and diastolic blood pressure and the pulse rate, and lower the activity of the blood coagulation factor VII-phospholipid complex. Further, omega-3 fatty acids seem to be well tolerated, without giving rise to any severe side effects.

The hypo-triglyceridemic effects of omega-3 oils from fish oils are well established. Amounts both above and below about 1 gram per day of omega-3 oils from fish oil have been shown to decrease serum triglyceride concentrations by about 25 % to about 40 %, decrease VLDL blood plasma levels, and to increase both LDl and HDL plasma levels (See e.g., Harris WS

1999 Clin Cardiol 22 (Suppl. II), p. 40-43). A dose-response relationship exists between omega-3 oil intake and triglyceride lowering. Postprandial triglyceridemia is especially sensitive to chronic omega-3 oil consumption (Kris-Etherton, et al., Circulation. 2002; 106:2747).

In addition, omega-3 oils obtained from fish have been described as being – like many fatty acids – weak PPAR alpha agonists in rodent models (see e.g., Keller et al 1993, PNAS, 90, p. 2160, and Larter et al, 2008, J. Gastroenterol. Hepatol. 23, p. 267). It is also known that fish oils mediate some of their effects, like increased beta oxidation of fatty acids (see e.g. Ren et al. 1997 J Bio Chem 272(43), p. 26827-32), or increase lipoprotein lipase enzyme activity, the enzyme critical for triglyceride clearance (Rudkowska et al 2010 Molecular Nutrition and Food Research 54(4), p. 543-50) in a PPAR alpha-dependent manner.

Omega-3 oils, omega-3 fatty acids, omega-3 esters, omega-3 alkyl esters or omega-3 mono-, di-, or tri-glycerides are well known in the art and are properly described in e.g. the patent application WO 2006/017698 which is incorporated into the present application by reference to this application.

An "omega-3 fatty acid" (also referred to as ω−3 fatty acids or n-3 fatty acids) is a n-3 polyunsaturated long-chain fatty acid (n-3 PUFA) and is defined to include any carboxylic acid having at least 15 carbon atoms and having at least 3 non-conjugated cis-unsaturated bonds, the distal one of which from the methyl end of the fatty acid chain being located between the third and fourth carbon atoms. The omega-3 fatty acids therefore include C_{16}-C_{24} alkanoic acids comprising 5-7 double bonds, wherein the last double bond is located between the third and fourth carbon atom from the methyl end of the fatty acid chain.

Examples of omega-3 fatty acids include, but are not limited to, stearidonic acid (SDA, C18:4), eicosatetraenoic acid (ETA, C20:4), eicosapentaenoic acid (EPA, C20:5), docosapentaenoic acid (DPA, C22:5), and docosahexaenoic acid (DHA, C22:6).

Terms such as "EPA" and "DHA" denote species of omega-3 oil and do not describe whether such oils exist as, for example, triglycerides, diglycerides, monoglycerides, free acids, esters, or salts.

Omega-3 fatty acids include synthetic or naturally occurring omega-3 fatty acids, such as those found in fish oil, marine mammal (e.g., seal) fat, cod liver oil, walnuts and walnut oil, wheat germ oil, rapeseed oil, soybean lecithin, soybeans, tofu, common beans, butternuts,

seaweed and flax seed oil. An omega-3 fatty acid may also be derived from genetically engineered sources such as transgenic plants. See, e.g., Frasier, et al., Nat Biotechnol. 2004 May 16.

The omega-3 fatty acids or their esters, derivatives, conjugates, precursors, salts and mixtures thereof can be used either in their pure form or as a component of an oil such as fish oil, preferably purified fish oil concentrates

An "omega-3 oil" is any oil comprising a source of omega-3 fatty acids, omega-3 esters, omega-3 alkyl esters, or omega-3 mono-, di-, or triglycerides, such as fish oil, marine mammal (e.g., seal) fat, cod liver oil, walnuts and walnut oil, wheat germ oil, rapeseed oil, soybean lecithin derived oils, soybean derived oils, tofu derived oils, common bean derived oils, butternut derived oils, seaweed derived oils, flax-borage oil, and flax seed oil. Omega-3 oils which can be used in making a pharmaceutical combination, such as a combined preparation or pharmaceutical composition, respectively, of the present invention include, but are not limited to omega-3 oil marketed under the tradenames Epax™ (Epax AS), Omegabrite™ (Omega Natural Science) and Epanova™ (Omthera Pharmaceuticals). Certain mixtures of esters, fatty acids, and/or mono- di- triglycerides may be specifically stated as oils according to the present invention. For example, a mixture consisting of omega-3 esters and fatty acids may be considered an omega-3 oil according to the present invention.

Omega-3 alkyl ester which can be used in making the pharmaceutical combination, such as a combined preparation or pharmaceutical composition, respectively, of the present invention include, but are not limited to, the omega-3 acid ethyl esters marketed under the trade names OMACOR® and/or LOVAZA™.

The term "E463808" is used to describe an omega-3 oil which has a composition comprising 46 % EPA, 38 % DHA, and 8 % other omega-3 oils (mass percent) where the EPA, DHA, and other omega-3 oils are present in the form of their ethyl esters.

The term "E681010"is used to describe an omega-3 oil which has a composition comprising 67.8 % EPA (mg/g), 9.9 %t DHA (mg/g), and about 9.6 % other omega-3 oils (mg/g), where the EPA, DHA, and other omega-3 oils are present in the form of ethyl esters.

Omega-3 alkyl esters include the ethyl esters of EPA and DHA. The E463808, OMEGA-3/90™ (K D Pharma), and Incromega™ (Croda Healthcare) omega-3 ethyl esters are several exemplary omega-3 alkyl esters.

The EPA:DHA ratio in an omega-3 oil as used in the present invention may be from 99:1 to 1 :99, preferably 4:1 to 1:4, more preferably 3:1 to 1:3, most preferably 2:1 to 1:2. In this context "EPA" and "DHA" can be present as free acids or esters or salts thereof.

The omega-3 fatty acids may comprise pure EPA or pure DHA, in the form of their free acids.

The omega-3 fatty acid or omega-3 oil composition optionally includes chemical antioxidants, such as alpha tocopherol, oils, such as soybean oil and partially hydrogenated vegetable oil, and lubricants such as fractionated coconut oil, lecithin and a mixture of the same. The most preferred form of omega-3 fatty acids is the Omacor™ omega-3 acid (K85EE, Pronova Biocare A.S., Lysaker, Norway).

Omega-3 esters may be formed by transesterification of an omega-3 oil and an alcohol and either an acid or reducing agent. Omega-3 alkyl ester may be formed by transesterifcation of an omega-3 oil and an alcohol (preferably methanol or ethanol) and either an acid or reducing agent. Because formation of lower alkyl esters is generally preferred, the alcohol preferably is a lower alkyl alcohol containing from 1 to 6 carbon atoms. More preferably, the alcohol is methanol (which reacts with glycerides to form methyl esters of the fatty acid residues) or ethanol (which reacts with glycerides to form ethyl esters of the fatty acid residues). Most preferably, the alcohol is ethanol.

Acid-catalyzed transesterification may be carried out, for example, by incubating a triglyceride at from about 0°C to about 150°C in a mixture containing the alcohol and an acid (e.g., HCl), preferably under a non- oxidizing atmosphere and in the absence of water. In one embodiment, the triglyceride/acid/alcohol mixture is refluxed for at least about 2 hours. In another embodiment, the triglyceride/acid/alcohol mixture is maintained at from about 0°C to about 50°C overnight. Methanol may be used to form methyl esters, and ethanol may be used to form ethyl esters. Because acid catalyzed transesterification is typically reversible, the alcohol preferably is present in a large excess so that the reaction proceeds essentially to completion. Preferably, the triglyceride concentration in the alcohol/acid mixture is from about 0.1 to about 15% by weight, and most preferably about 3% by weight. If the acid is HCl, the concentration of HCl in the alcohol/HCl mixture preferably is from about 4 to about 15% by weight, and most preferably about 10% by weight. Such a mixture may be prepared by various methods known in the art, such as bubbling dry gaseous hydrogen chloride into dry ethanol, or adding 1 mL of acetylchloride to each 10 mL of alcohol (to form approximately 10% by weight HCl in alcohol). Although HCl is most preferred, other acids may alternatively

be used. One such acid is sulfuric acid, which typically is used at a concentration of from about 0.5 to about 5% by weight in the alcohol. It should be noted, however, that because sulfuric acid is a strong oxidizing agent, it preferably is not used with long reflux times (i.e., greater than about 6 hours), at high concentrations (i.e., greater than about 5% by weight), or at high temperatures (i.e., greater than 150° C.). Another example of a suitable acid is boron trifluoride, which preferably is used at a concentration of from about 1 to about 20% by weight in the alcohol. Boron trifluoride, however, is less preferred than HCl because boron trifluoride has a greater tendency to produce undesirable byproducts.

In base-catalyzed transesterification, the omega-3 oil is transesterified by an alcohol in the presence of a basic catalyst. In this instance, the base may be, for example, sodium methoxide, potassium methoxide, elemental sodium, sodium hydroxide, or potassium hydroxide. Preferably, the volumetric ratio of omega-3 oil to the base/alcohol mixture is at least about 1:1, and most preferably about 1:2. The concentration of the base in the alcohol preferably is from about 0.1 to about 2 M. The base-catalyzed transesterification reaction can be conducted at room temperature (i.e., at a temperature of from about 20° to about 25°C) for from about 6 to about 20 hours. Alternatively, the base-catalyzed transesterification reaction is conducted at a temperature greater than room temperature.

The glyceride/alcohol/catalyst solution preferably is heated to a temperature of at least about 40°C, more preferably from about 70 to about 150°C, and most preferably at about 100°C. The solution can be heated using a reflux condenser so that the reaction mixture may be heated to temperatures above the boiling point of one or more components in the mixture without losing the components into the vapor phase (i.e., when the components vaporize, they rise into the reflux condenser which has a cooler temperature, thereby causing the vapor to condense into a liquid and flow back into the liquid mixture).

During the transesterification reaction, the reacting mixture is preferably placed under a non-oxidizing atmosphere, such as an atmosphere consisting essentially of a noble gas, N_2, or a combination thereof. Use of such an atmosphere is particularly preferred if the transesterification reaction is conducted over a period of time exceeding about 10 minutes. An oil- soluble antioxidant (e.g., ascorbyl palmitate or propyl gallate) may also be added to the reacting mixture to prevent auto-oxidation, and is particularly preferred where a non-oxidizing atmosphere is not used.

Oil purity is also an important aspect of the present invention. Oil purity is defined as a percentage (e.g., by volume or by weight) of one component with respect to the entire oil

composition. Several examples of oil components include, but are not limited to, monoglycerides, diglycerides, triglycerides, free acids, esters, and derivatives, precursors, and salts thereof. For example, an ester oil with a purity of 95 percent by weight comprises at least 95 percent esters. The remaining percentage may comprise free acids, mono- di- and/or triglycerides, or other components. As another example, an omega-3 ester oil with a purity of 90 percent by weight comprises at least 90 percent omega-3 esters and the remaining percentage can comprise any one or more of other oil components. A mixture of species of one component (e.g. C8 and C10 esters) need not be discerned in the determination of purity. However, a distinction of specific species within a component (e.g., C8 and C10 esters) can also be included in specific embodiments of the present invention.

According to the present invention, omega-3 oils with a purity greater than about 85 percent, 90 percent, 91 percent, 92 percent, 93 percent, 94 percent, 95 percent, 96 percent, 97 percent, 98 percent, 99 percent or more are preferred. Omega-3 oils with a high purity of omega-3 esters are preferred. According to the present invention, omega-3 oils with a high purity comprise greater than about 85 percent, 90 percent, 91 percent, 92 percent, 93 percent, 94 percent, 95 percent, 96 percent, 97 percent, 98 percent, 99 percent or more of one component by weight or by volume.

Preferred omega-3 esters include, but are not limited to, EPA and DHA. Other preferred omega-3 esters include omega-3 ethyl esters.

Oil composition is another important aspect of the present invention. Oil composition can be described as both the species and the components of an oil. Species include specific omega-3 oils such as, but not limited to, EPA, DHA, linoleic acid, linolenic acid, etc. Components include, but are not limited to, monoglycerides, diglycerides, triglycerides, free acids, esters, and derivatives, precursors, and salts thereof. For example, E463808 comprises about 46 % EPA and about 38 % DHA (mass percent) as ethyl esters. The remaining portion consists essentially of omega-3 oils other than EPA and DHA and other non-omega-3 oils. Other commercially available omega-3 oils contain higher or lower levels of total EPA and DHA as components such as monoglycerides, diglycerides, triglycerides, esters, free acids, etc. or mixtures thereof. Omega-3 oils with a composition comprising a mass percent of EPA and DHA equal to or greater than about 55 percent or greater than about 75 percent or greater than about 80 percent are preferred.

Mixtures of omega-3 alkyl esters with other forms of omega-3 oil (e.g., fatty acids, triglycerides) are included, according to the present invention. Oils containing highly pure or pure alkyl esters are included in the present invention.

In another embodiment, the purity of omega-3 esters or omega-3 alkyl esters is at least about 50 percent by weight, at least about 60 percent by weight, at least about 70 percent by weight, at least about 75 percent by weight, at least about 80 percent by weight, or at least about 85 percent by weight. In another embodiment, the purity of omega-3 esters or omega-3 alkyl esters is about 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 99 percent or more by weight. In another embodiment, the purity of omega-3 esters or omega-3 alkyl esters is between about 25 and about 100 percent by weight, between about 40 and about 100 percent by weight, between about and about 100 percent by weight, between about 60 and about 100 percent by weight, between about 70 and about 100 percent by weight, between about 75 and about 100 percent by weight, between about 75 and about 95 percent by weight, between about 75 and about 90 percent by weight, or between about 80 and about 85 percent by weight. In another embodiment, the purity of omega-3 esters or omega-3 alkyl esters is about 100 percent by weight, about 99 percent by weight, about 96 percent by weight, about 92 percent by weight, about 90 percent by weight, about 85 percent by weight, about 80 percent by weight, about 75 percent by weight, about 70 percent by weight, about 65 percent by weight, about 60 percent by weight, about 55 percent by weight, or about 50 percent by weight.

In another embodiment, the oil composition comprising EPA and DHA is at least about 50 percent by weight, at least about 60 percent by weight, at least about 70 percent by weight, at least about 75 percent by weight, at least about 80 percent by weight, or at least about 84 percent by weight. In another embodiment, the oil composition comprising EPA and DHA is about 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, or 95 percent by weight. In another embodiment, the oil composition comprising EPA and DHA is between about 25 and about 95 percent by weight, between about 40 and about 95 percent by weight, between about 50 and about 95 percent by weight, between about 60 and about 95 percent by weight, between about 70; and about 95 percent by weight, between about 75 and about 95 percent by weight, : between about 75 and about 90 percent by weight, between about 75 and about 8S percent by weight, or between about 80 and about 85 percent by weight. In another embodiment, the oil composition comprising EPA and DHA is about 99 percent by weight, about 96 percent by weight, about 92 percent by weight, about 90 percent by weight, about 84 percent by weight, about 80 percent by weight, about 75 percent by weight, about 70

percent by weights about 65 percent by weight, about 60 percent by weight, about 55 percent by weight, or about 50 percent by weight.

In another embodiment, the omega-3 ester or omega-3 alkyl ester has about a 23:19 ratio of EPA:DHA, about a 75:11 ratio of EPA:DHA, about a 95:1 ratio of EPA:DHA, about a 9:2 ratio of EPA:DHA, about a 10:1 ratio of EPA:DHA, about a 5:1 ratio of EPA:DHA, about a 3:1 ratio of EPA:DHA, about a 2:1 ratio of EPA:DHA, about a 1:1 ratio of EPA:DHA, about a 1:2 ratio of EPA:DHA, about a 1:3 ratio of EPA:DHA, or about a 1:5 ratio of EPA:DHA. In another embodiment, the omega-3 ester or omega-3 alkyl ester has about a 95:1 ratio of EPA:DHA, about a 75:1 ratio of EPA:DHA, about a 50:1 ratio of EPA:DHA, about a 25:1 ratio of EPA:DHA, about a 20:1 ratio of EPA:DHA, about a 15:1 ratio of EPA:DHA, about a 10:1 ratio of EPA:DHA, about a 7.5:1 ratio of EPA:DHA, about a 5:1 ratio of EPA:DHA, about a t 4:1 ratio of EPA:DHA, about a 3:1 ratio of EPA:DHA, about a 2:1 ratio of EPA:DHA, about a 1.5: 1 ratio of EPA:DHA, about a 1: 1 ratio of EPA:DHA, about a 1: 1.5 ratio of EPA:DHA, about a 1:2 ratio of EPA:DHA, about a 1:3 ratio of EPA:DHA, or about a I 1:5 ratio of EPA:DHA. In another embodiment, the omega-3 ester or omega-3 alkyl ester has from about a 95:1 ratio to about a 1:5 ratio of EPA:DHA, from about a 50:1 ratio to about a 1:1 ratio of EPA:DHA, from about a 25:1 ratio to about a 1:1 ratio of EPA:DHA, from about a 10: 1 ratio to about a 1: 1 ratio of EPA:DHA, from about a 5:1 ratio to about a 1:1 ratio of EPA:DHA, from about a 3:1 ratio to about a 1:1 ratio of EPA:DHA, from about a 2:1 ratio to about a 1:1 ratio of EPA:DHA, or from about a i 1.5:1 ratio to about a 1:1 ratio of EPA:DHA. In another embodiment, the omega-3 ester or omega-3 alkyl ester has at least about a 1:5 ratio of EPA:DHA, at least about a 1: 1 ratio of EPA:DHA, at least about a 1.5: 1 ratio of EPA:DHA, at least about a 2: 1 ratio of EPA:DHA, at least about a 3:1 ratio of EPA:DHA, at least about a 5:1 ratio of EPA:DHA, or at least about a 10:1 ratio of EPA:DHA.

Example of preferred specific ratio, composition, or purity of omega-3 oil is for example an omega-3 oil comprising at least 90 percent (w/w) omega-3 ethyl esters with approximately 46.5 percent EPA and approximately 37.5 percent DHA (e.g., OMACOR or LOVAZA).
Other preferred commercially available omega-3 oils are for example those available from Croda International (England) and Pronova Biocare (Norway).

The dosage of omega-3 oil administered will also be generally dependent upon the health of the subject being treated, the extent of treatment desired, the nature and kind of concurrent therapy, if any, and the frequency of treatment and nature of the effect desired.

A therapeutically acceptable daily dosage of omega-3 oil has been recommended or considered via several national and international groups including, but not limited to, the American Heart Association (AMA) and the International Society for the Study of Fatty Acids and lipids (ISSFAL).

Table 1 includes daily dosage amounts of omega-3 as considered/recommended via several organizations.

Omega-3 dose (grams)/day	Comment
0. 65	ISSFAL consideration (1999)
1.0	AHA recommended (2000, 2004)
1.8	Omacor ® dose
3.0	FDA limit on daily consumption
3.6	Omacor ® dose

In general, the dosage of the omega-3 oils is generally in the range of from about 0.001 to about 100 mg/kg body weight of the subject per day, preferably from about 0.1 to about 50 mg/kg body weight of the subject per day, administered as a single or divided dose. However, some variability in the general dosage range may also be required depending upon the age, weight, and species of the patient, the intended route of administration, and the progress and degree of severity of the disease or condition being treated.

The dosage of omega-3 fatty acids, omega-3 esters, omega-3 alkyl esters or omega-3 mono-, di-, or tri-glycerides, administered will also be generally dependent upon the health of the subject being treated, the extent of treatment desired, the nature and kind of concurrent therapy, if any, and the frequency of treatment and nature of the effect desired.

Daily dosages of omega-3 oil required in practicing the method of the present invention will vary depending upon, for example the mode of administration and the severity of the condition to be treated. An indicated daily dose is in the range of from about 100 to about 5000 mg, e.g. from about 100 to about 4000 mg or e.g. from about 200 to about 4000 mg or e.g. from about 500 to about 4000 mg, or e.g. between 500 to 2000 mg of active agent for oral use, conveniently administered once or in divided dosages.

In one embodiment of the invention the omega-3 oil suitable for use in the pharmaceutical combination, such as a combined preparation or pharmaceutical composition, respectively, of the present invention comprises at least 90 percent (w/w) omega-3 ethyl esters with about 46.5 percent EPA and 37.5 percent DHA (e.g., OMACOR) and the daily dose is in the range from about 100 to about 5000 mg, e.g. from about 500 to about 5000 mg or e.g. from about

1000 to about 5000 mg or e.g. from about 1000 to about 4000 mg, or e.g. between 1500 to 4000 mg of active agent for oral use, conveniently administered once or in divided dosages.

Other omega-3 oils that may be suitable for use in the pharmaceutical combination, such as a combined preparation or pharmaceutical composition, respectively, of the present invention include, but are not limited to, Epax®, Omegabrite®, Epanova®, E463808, E681010, Omacor®, LOVAZA®, OMEGA- 3/90, Incromega, Epadel®, Seacor®, Esapent® and Eskimo®.

Epadel (ethyl icosapentate) (Mochida; Tokyo, Japan) is an ethical drug containing highly purified (>98%) fish-derived ethyl EPA, which is currently indicated in Japan for the treatment of arteriosclerosis and hyperlipidemia. Preferably the daily dosage is between 500 and 4000 mg of EPA preferably e.g. 1800 mg/day.

"Eskimo-3® brand Fish Oil 4.6 g" provides omega-3 fatty acids including 645-830 mg EPA (eicosapentaenoic acid) and 380-540 mg DHA (docosahexaenoic acid) - Serving Size: 1 teaspoon (5 mL).

"Eskimo Kids®" comprises Vitamin D (as Cholecalciferol) 100 IU, Omega-3 Fatty Acids 800 mg, EPA (eicosapentaenoic acid) 270 mg, DHA (docosahexaenoic acid) 180 mg, Canola Oil Containing: (Oleic Acid, Linoleic Acid, Alpha-Linolenic Acid) 2g - Serving Size: 1 Teaspoon (5 mL).

Seacor®, Esapent®, Eskim® are n-3 PUFA and administered preferably at a dose of 500 to 3000 mg a day preferably e.g. 1 g once a day. Eskim® contains omega-3 triglycerides (DHA, EPA) and is marketed by Sigma Tau S.p.A in Italy.

Epax® (EPAX AS): Epax is a brand of different Omega-3 oils. E.g. Epax Omega-3 Joint Formula contains is in the form of a easy-to-swallow softgels containing 1000 mg of Omega 3 fish oil, which contains around 375 mg of EPA and around 67 mg of DHA. Other preferred Epax products are Epax 6000 TG, Epax 6000 EE, Epax 5500 TG, Epax 5500 EE.

Combinations

Hence, one embodiment of the present invention pertains to a pharmaceutical combination, such as a combined preparation or pharmaceutical composition, respectively, separately or together, in particular for the prevention, delay of progression or treatment of

hypertriglyceridemia, in particular chylomicronemia (also called hyperchylomicronemia) comprising

at least one DGAT1 inhibitor or a pharmaceutically acceptable salt or ester thereof,

at least one kind of triglyceride lowering drug selected from the group consisting of

(a) at least one PPAR alpha agonist or a pharmaceutically acceptable salt thereof or ester thereof, and

(b) at least one compound selected from the group consisting of

(i) natural or synthetic omega-3 fatty acids or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof, and

(ii) omega-3 oils,

and (c) optionally at least one pharmaceutically acceptable carrier.

In one embodiment of the invention the pharmaceutical combination, such as a combined preparation or pharmaceutical composition, respectively, separately or together, in particular for the prevention, delay of progression or the treatment of hypertriglyceridemia, in particular chylomicronemia (also called hyperchylomicronemia) comprises at least one DGAT1 inhibitor, or a pharmaceutically acceptable salt thereof or ester thereof – as set out herein before – and at least one PPAR alpha agonist or a pharmaceutically acceptable salt thereof.

Alternatively, the pharmaceutical combination, such as a combined preparation or pharmaceutical composition, respectively, separately or together, in particular for the prevention, delay of progression or the treatment of hypertriglyceridemia, in particular chylomicronemia (also called hyperchylomicronemia) comprises at least one DGAT1 inhibitor, or a pharmaceutically acceptable salt thereof or ester thereof – as set out herein before – and at least one compound selected from the group consisting of

(i) natural or synthetic omega-3 fatty acids or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof, or

(ii) omega-3 oils.

In a further aspect the DGAT1 inhibitor useful in the pharmaceutical combination of the present invention is a compound which is selected from:

4-[4-[5-[[6-(Trifluoromethyl)-3-pyridinyl]amino]-2-pyridinyl]phenyl]cyclohexyl-acetic acid,

(4-{4-[5-(Benzo[d]oxazol-2-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid,

(4-{6-[5-(4-Chloro-phenyl)-[1,3,4]oxadiazol-2-yl]-1H-benzoimidazol-2-yl}-3,5-dimethyl-phenoxy)-acetic acid,

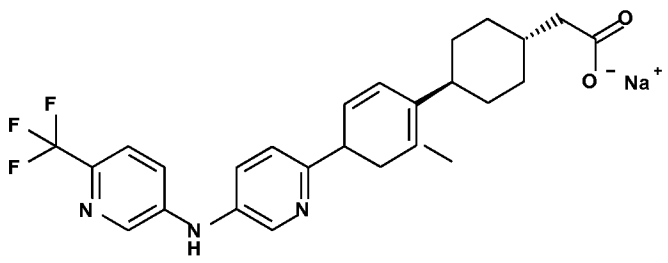
(3,5-Dichloro-4-{6-[5-(4-chloro-phenyl)-[1,3,4]oxadiazol-2-yl]-1H-benzoimidazol-2-yl}-phenoxy)-acetic acid,

3-(4-{6-[5-(4-Methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-1H-benzoimidazol-2-yl}-3,5-dimethyl-phenyl)-propionic acid,
3-(4-{6-[5-(3-Chlorophenylamino)-[1,3,4]oxadiazol-2-yl]-1H-benzoimidazol-2-yl}-3,5-dimethylphenyl)-propionic acid,
3-(4-{6-[5-(4-methoxyphenylamino)-[1,3,4]oxadiazol-2-yl]-1H-benzimidazol-2-yl}-3,5-dimethylphenyl)-propionic acid,
3-(4-{6-[5-(4-Chloro-phenyl)-[1,3,4]oxadiazol-2-yl]-1H-benzoimidazol-2-yl}-3,5-dimethyl-phenyl)-propionic acid,
3-(4-{5-[5-(4-Methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-1H-benzoimidazol-2-yl}-3,5-dimethyl-phenyl)-2,2-dimethyl-propionic acid,
[3-(4-{6-[5-(4-Chloro-phenyl)-[1,3,4]oxadiazol-2-yl]-1H-benzoimidazol-2-yl}-3,5-dimethyl-phenyl)-propyl]-phosphonic acid,
(3-{3,5-Dimethyl-4-[6-(5-phenyl-[1,3,4]oxadiazol-2-yl)-1H-benzoimidazol-2-yl]-phenyl}-propyl)-phosphonic acid,
[3-(4-{6-[5-(4-Methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-1H-benzoimidazol-2-yl}-3,5-dimethyl-phenyl)-propyl]-phosphonic acid,
3-{4-[6-(5-methoxy-[1,3,4]oxadiazol-2-yl)-1H-indol-2-yl]-3,5-dimethylphenyl}-propionic acid and
3-(3,5-Dichloro-4-{6-[5-(4-chloro-phenyl)-[1,3,4]oxadiazol-2-yl]-1H-benzoimidazol-2-yl}-phenyl)-propionic acid,
or a pharmaceutically acceptable salt thereof or ester thereof.

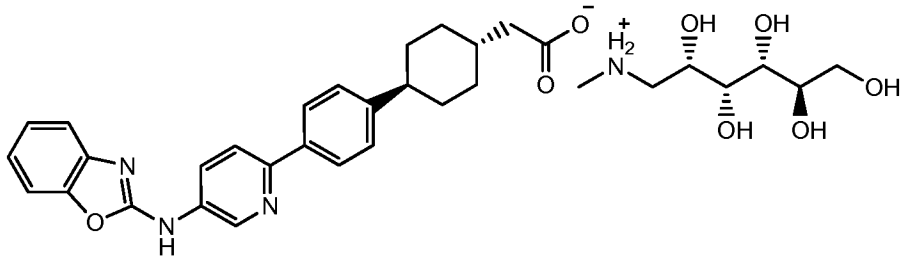
In one embodiment the DGAT1 inhibitor is selected from (4-{4-[5-(6-Trifluoromethyl-pyridin-3-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid, or a pharmaceutically acceptable salt or ester thereof, and (4-{4-[5-(Benzo[d]oxazol-2-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid or a pharmaceutically acceptable salt or ester thereof.

In a further aspect of the invention the DGAT1 inhibitor useful in the pharmaceutical combination of the present invention is trans-4-[4-[5-[[6-(trifluoromethyl)-3-pyridinyl]amino]-2-pyridinyl]phenyl]cyclohexane acetic acid, or a pharmaceutically acceptable salt thereof.

In another aspect of this embodiment of the invention the DGAT1 inhibitor useful in the pharmaceutical composition of the present invention is trans-4-[4-[5-[[6-(trifluoromethyl)-3-pyridinyl]amino]-2-pyridinyl]phenyl]cyclohexane acetic acid, sodium salt:



In another aspect of this embodiment the DGAT1 inhibitor is 2-((1R,4R)-4-(4-(5-(benzo[d]oxazol-2-ylamino)pyridin-2-yl)phenyl)cyclohexyl)acetic acid or a pharmaceutically acceptable salt or ester thereof. In another embodiment, the DGAT1 inhibitor is 2-((1R,4R)-4-(4-(5-(benzo[d]oxazol-2-ylamino)pyridin-2-yl)phenyl)cyclohexyl)acetic acid meglumine salt. In particular, the DGAT-1 inhibitor is of the following formula:



In one embodiment of the present invention, the PPAR alpha agonist useful in the pharmaceutical combination of the present invention is a fibrate. In one aspect of this embodiment the fibrate is selected from the group consisting of clofibrate, gemfibrozil, fenofibrate, micronized fenofibrate, fenofibric acid, ciprofibrate and bezafibrate.

In another aspect, the fibrate useful in the pharmaceutical combination of the present invention is fenofibrate, fenofibric acid or micronized fenofibrate.

In a further embodiment of the invention the omega-3 fatty acid useful in the pharmaceutical combination of the present invention may be selected from the group consisting of natural or synthetic omega-3 fatty acids or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof, and omega-3 oils as defined herein above. In one embodiment the omega-3 fatty acids or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof, are EPA or DHA or mixtures thereof.

In another aspect of the invention the omega-3 acid or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof, may be selected from

EPA or DHA or mixtures thereof. In one embodiment the ratio EPA:DHA is from about 99:1 to about 1:99. In another embodiment the ratio EPA:DHA is from about 2:1 to about 1:2.

In one embodiment of the invention the omega-3 acid or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof, is a mixture of EPA and DHA. In another embodiment of the invention the omega-3 oil comprises a mixture of the omega-3 acids or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof, such as EPA and DHA and other omega-3 oils. In one aspect of this embodiment the omega-3 oil comprises omega-3 acid ethyl ester.

In a further embodiment of the invention the omega-3 oil is for example an omega-3 oil comprising at least 90 percent (w/w) omega-3 ethyl esters with about 46.5 percent EPA and about 37.5 percent DHA (e.g., OMACOR™, LOVAZA™).

In one embodiment of the invention the pharmaceutical combination, such as a combined preparation or pharmaceutical composition, respectively of the present invention is for simultaneous, separate or sequential use.

In one embodiment of the invention the pharmaceutical combination is a combined preparation or a fixed combination. The combination may comprise some or all of the active ingredients. For example, in one embodiment, the DGAT1 inhibitor and PPAR alpha agonist are present in one combined preparation whereas the natural or synthetic omega-3 fatty acids or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof, or omega-3 oils, is a separate component. In an alternative embodiment the DGAT1 inhibitor is present in a combined preparation with the natural or synthetic omega-3 fatty acids or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof, or omega-3 oils, and the PPAR alpha agonist is a separate component. In another embodiment, the PPAR alpha agonist is present in a combined preparation with the natural or synthetic omega-3 fatty acids or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof, or omega-3 oils, and the DGAT1 inhibitor is a separate component. According the combination of the present invention can comprise each class of active in a separate dosage form or two or more classes of the active can be combined into one dosage form.

In a further embodiment of the invention the pharmaceutical combination such as a combined preparation or pharmaceutical composition, respectively of the present invention is a combined preparation for simultaneous, separate or sequential use.

Typical dosage ranges for each of the components of the pharmaceutical combination of the present invention are set forth below, as well as in the specific sections above in relation to each class of active ingredient:

Dosage ranges for the DGAT1 inhibitor include, for example, from about 0.01 mg to about 2000 mg per day, e.g. 0.01, 0.05, 0.1, 0.2, 0.5, 1.0, 2.5, 5, 10, 15, 20, 25, 30, 40, 50, 75, 100, 125, 150, 175, 200, 225, 250, 500, 750, 850, 1,000 and 2,000 milligrams per day, more particularly from about 5 mg/day to about 100 mg/day, from about 10 mg/day to about 40 mg/day, or from about 20 mg/day to about 40 mg/day or 5, 10, 15, 20, 25, 30, 35, 40, 80 or 100 mg/day.

Dosage ranges for the fibrates range from about 20 mg/day to about 2500 mg/day, more particularly from about 40 mg/day to about 2000 mg/day, for example 20, 30, 40, 50, 60, 70, 80 , 90, 100, 150, 200, 500, 1000, 1500 or 2000 mg/day.

For example, fenofibrate may be administered with a dose from about 20 mg/day to about 200 mg/day, such as 35 mg/day, 40 mg/day, 43 mg/day, 48 mg/day, 50 mg/day, 54 mg/day, 67 mg/day, 130 mg/day, 145 mg/day, 150 mg/day, 160 mg/day or 200 mg/day. Fenofibric acid may be administered, for example, with a dose from about 45 mg/day to about 135 mg/day, such as 45 mg/day or 135 mg/day. For example clofibrate may be administered with a dose from about 500 mg/day to about 2000 mg/day, for example, 2000 mg/day administered in divided doses, such as 500 mg 4 times/day; For example Gemfibrozil may be administered with a dose from about 600 mg/day to about 1200 mg/day for example, 1200 mg/day administered in divided doses, such as 600 mg 2 times/day.

Dosage ranges for the natural or synthetic omega-3 fatty acids or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof, or the omega-3 oils range from about 100 mg/day to about 5000 mg/day, e.g. from about 100 mg/day to about 4000 mg/day or e.g. from about 200 mg/day to about 4000 mg/day or e.g. from about 500 mg/day to about 4000 mg/day, or e.g. from about 500 mg/day to about 2000 mg/day, for example 1000 mg/day, 1800 mg/day or 4000 mg/day conveniently administered once or in divided dosages. For example Omacor™ may be administered with a dose from about 2000 mg/day to about 4000 mg/day for example, 4000 mg/day administered once or in divided dosages such as 2000 mg 2 times/day.

Furthermore, the present invention relates to a “kit of parts” in the sense that the combination partners as defined above can be dosed independently or by use of different fixed combinations with distinguished amounts of the combination partners as defined above, i.e. simultaneously or at different time points. The parts of the kit of parts can then, e.g., be administered simultaneously or chronologically staggered, that is at different time points and with equal or different time intervals for any part of the kit of parts.

Preferably, the time intervals are chosen such that the effect on the treated disease or condition in the combined use of the parts is larger than the effect which would be obtained by use of only any one of the components.

The ratio of the total amounts of the combination partners to be administered in the combined preparation or kit of parts can be varied, e.g. in order to cope with the needs of a patient sub-population to be treated or the needs of the single patient which different needs can be due to age, sex, body weight, etc. of the patients.

The present invention thus also provides a kit of parts comprising
at least one DGAT1 inhibitor, or a pharmaceutically acceptable salt thereof or ester thereof and
at least one kind of triglyceride lowering drug selected from the group consisting of

(a) at least one PPAR alpha agonist or a pharmaceutically acceptable salt thereof or ester thereof, and
(b) at least one compound selected from the group consisting of
    (i) natural or synthetic omega-3 fatty acids or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof, and
    (ii) omega-3 oils,

and optionally at least one pharmaceutically acceptable carrier, in the form of two or three or more separate units of the components.

In one embodiment, the DGAT1 inhibitor is trans-4-[4-[5-[[6-(trifluoromethyl)-3-pyridinyl]amino]-2-pyridinyl]phenyl]cyclohexane acetic acid, or a pharmaceutically acceptable salt thereof or trans-4-[4-[5-[[6-(trifluoromethyl)-3-pyridinyl]amino]-2-pyridinyl]phenyl]cyclohexane acetic acid, sodium salt and the PPAR alpha agonist is a fibrate, selected from the group consisting of fenofibrate, micronized fenofibrate, fenofibric acid, bezafibrate, gemfibrozil, clofibrate and ciprofibrat, more preferably fenofibrate, micronized fenofibrate or fenofibric acid.

In another embodiment, the DGAT1 inhibitor is 2-((1R,4R)-4-(4-(5-(benzo[d]oxazol-2-ylamino)pyridin-2-yl)phenyl)cyclohexyl)acetic acid or a pharmaceutically acceptable salt or ester thereof, or 2-((1R,4R)-4-(4-(5-(benzo[d]oxazol-2-ylamino)pyridin-2-yl)phenyl)cyclohexyl)acetic acid meglumine salt and the PPAR alpha agonist is a fibrate, selected from the group consisting of fenofibrate, micronized fenofibrate, fenofibric acid, bezafibrate, gemfibrozil, clofibrate and ciprofibrat, more preferably fenofibrate, micronized fenofibrate or fenofibric acid.

Preferably the omega-3 acid or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof, is a mixture of EPA and DHA.

In another embodiment of the invention the omega-3 oil comprises a mixture of the omega-3 acids or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof, such as EPA, DHA and other omega-3 oils. In one aspect the omega-3 oil comprises omega-3 acid ethyl ester.

The invention furthermore relates to a commercial package comprising the combination according to the present invention together with instructions for simultaneous, separate or sequential use.

Preferably, there is at least one beneficial effect, e.g. an additive, or even a mutual enhancing of the effect of the combination partners according to the invention, in particular a synergism (e.g., a more than additive effect), or other additional advantageous effects, less side effects, a combined therapeutic effect in a non-effective dosage of the combination partners, and very preferably a strong synergism of the combination partners.

The person skilled in the pertinent art is fully enabled to select a relevant animal test model to prove the hereinbefore and hereinafter indicated therapeutic indications and beneficial effects. The pharmacological activity may, for example, be demonstrated following essentially an *in vivo* test procedure in mice or in a clinical study as described hereinafter.

It will be understood that references to the combination partners are meant to also include the pharmaceutically acceptable salts. If these combination partners have, for example, at least one basic center, they can form acid addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The combination partners having an acid group (for example COOH) can also form salts with bases. The

combination partners or a pharmaceutically acceptable salt thereof may also be used in form of a hydrate or include other solvents used for crystallization.

The term "pharmaceutically acceptable", as used herein, refers to those compounds, materials, compositions and/or dosage forms, which are, within the scope of sound medical judgment, suitable for contact with the tissues of mammals, especially humans, without excessive toxicity, irritation, allergic response and other problem complications commensurate with a reasonable benefit/risk ratio.

By the term "treatment" is understood the management and care of a patient for the purpose of combating the disease, condition, or disorder.

The term "prevention" means prophylactic administration of the combination to healthy patients to prevent the outbreak of the conditions mentioned herein. Moreover, the term "prevention" means prophylactic administration of such combination to patients being in a pre-stage of the conditions to be treated.

The term "delay of progression" used herein means administration of the combination, such as a combined preparation or pharmaceutical composition, to patients being in a pre-stage of the condition to be treated in which patients a pre-form of the corresponding condition is diagnosed.

The structure of the active agents identified by code nos., generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g., Patents International, e.g., IMS World Publications. The corresponding content thereof is hereby incorporated by reference. Any person skilled in the art is fully enabled to identify the active agents and, based on these references, likewise enabled to manufacture and test the pharmaceutical indications and properties in standard test models, both in vitro and in vivo.

The term "synergistic" shall mean that the drugs, when taken together, produce a total joint effect that is greater than the sum of the effects of each drug when taken alone.

Determining a synergistic interaction between one or more components, the optimum range for the effect and absolute dose ranges of each component for the effect may be definitively measured by administration of the components over different w/w ratio ranges and doses to patients in need of treatment. For humans, the complexity and cost of carrying out clinical

studies on patients renders impractical the use of this form of testing as a primary model for synergy. However, the observation of synergy in one species can be predictive of the effect in other species and animal models exist, as described herein, to measure a synergistic effect and the results of such studies can also be used to predict effective dose and plasma concentration ratio ranges and the absolute doses and plasma concentrations required in other species by the application of pharmacokinetic/pharmacodynamic methods.

The pharmaceutical compositions according to the invention can be prepared in a manner known per se and are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals (warm-blooded animals), including man, comprising a therapeutically effective amount of the pharmacologically active compound, alone or in combination with one or more pharmaceutically acceptable carries, especially suitable for enteral or parenteral application.

The novel pharmaceutical preparations of the invention contain, for example, from about 10% to about 100%, e. g. 80% or 90%, or from about 20% to about 60%, of the active ingredients.

Pharmaceutical preparations according to the invention for enteral or parenteral administration are, e.g., those in unit dose forms, such as sugar-coated tablets, tablets, capsules, bars, sachets, granules, syrups, aqueous or oily suspensions or suppositories and furthermore ampoules. These are prepared in a manner known per se, e. g. by means of conventional mixing, granulating, sugar-coating, dissolving or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active ingredient with solid carriers, if desired granulating a mixture obtained, and processing the mixture or granules, if desired or necessary, after addition of suitable excipients to give tablets or sugar-coated tablet cores.

Tablets may be formed from a mixture of the active compounds with fillers, for example calcium phosphate; disintegrating agents, for example maize starch, lubricating agents, for example magnesium stearate; binders, for example microcrystalline cellulose or polyvinylpyrrolidone and other optional ingredients known in the art to permit tabletting the mixture by known methods. Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by known methods. The contents of the capsule may be formulated using known methods so as to give sustained release of the active compound.

Other dosage forms for oral administration include, for example, aqueous suspensions containing the active compounds in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxymethylcellulose, and oily suspensions containing the active compounds in a suitable vegetable oil, for example arachis oil.

The active compounds may be formulated into granules with or without additional excipients. The granules may be ingested directly by the patient or they may be added to a suitable liquid carrier (e.g. water) before ingestion. The granules may contain disintegrants, e.g. an effervescent pair formed from an acid and a carbonate or bicarbonate salt to facilitate dispersion in the liquid medium.

In the compositions, the components can be administered together, one after the other or separately in one combined unit dose form, in two separate unit dose forms or in three separate unit dose forms.

In one embodiment of the invention, the unit dose form is a fixed combination. In a fixed combination the components are administered in the form of a single galenic formulation, e. g. a single tablet or a single infusion.

Therapeutic Uses

A further aspect of the present invention is the use of a pharmaceutical combination, such as a combined preparation or pharmaceutical composition, respectively, according to the present invention comprising at least one DGAT1 inhibitor, or a pharmaceutically acceptable salt thereof or ester thereof and at least one kind of triglyceride lowering drug selected from the group consisting of

(a) at least one PPAR alpha agonist or a pharmaceutically acceptable salt thereof or ester thereof, and
(b) at least one compound selected from the group consisting of
    (i) natural or synthetic omega-3 fatty acids or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof, and
    (ii) omega-3 oils,

and optionally at least one pharmaceutically acceptable carrier for the prevention, delay of progression or the treatment of a disease or condition associated with lipid metabolism and cell proliferation of humans and other species, e.g. metabolic disorders such as obesity, diabetes, anorexia nervosa, bulimia, cachexia, syndrome X, insulin resistance, hypoglycemia, hyperglycemia, hyperuricemia, hyperinsulinemia, hypercholesterolemia, hyperlipidemia, dyslipidemia, mixed dyslipidemia, hypertriglyceridemia, pancreatitis, and

nonalcoholic fatty liver disease; cardiovascular diseases, such as atherosclerosis, arteriosclerosis, acute heart failure, congestive heart failure, coronary artery disease, cardiomyopathy, myocardial infarction, angina pectoris, hypertension, hypotension, stroke, ischemia, ischemic reperfusion injury, aneurysm, restenosis, and vascular stenosis; neoplastic diseases, such as solid tumors, skin cancer, melanoma, lymphoma, and endothelial cancers, for example, breast cancer, lung cancer, colorectal cancer, stomach cancer, other cancers of the gastrointestinal tract (for example, esophageal cancer and pancreatic cancer), prostate cancer, kidney cancer, liver cancer, bladder cancer, cervical cancer, uterine cancer, testicular cancer, and ovarian cancer; dermatological conditions, such as acne vulgaris, more especially hypertriglyceridemia, in particular chylomicronemia (also called hyperchylomicronemia), such as familial chylomicronemia syndrome (FCS) or Type V, Type IV or mutifactorial hyperlipoproteinemia (also known as non-FCS).

As set out before, the DGAT1 inhibitor is preferably selected from (4-{4-[5-(6-Trifluoromethyl-pyridin-3-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid, or a pharmaceutically acceptable salt or ester thereof, and (4-{4-[5-(Benzo[d]oxazol-2-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid or a pharmaceutically acceptable salt or ester thereof.

A further aspect of the present invention is the use of a pharmaceutical combination, such as a combined preparation or pharmaceutical composition, respectively, according to the present invention comprising at least one DGAT1 inhibitor, or a pharmaceutically acceptable salt thereof or ester thereof and at least one kind of triglyceride lowering drug selected from the group consisting of

(a) at least one PPAR alpha agonist or a pharmaceutically acceptable salt thereof or ester thereof, and
(b) at least one compound selected from the group consisting of
    (i) natural or synthetic omega-3 fatty acids or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof, and
    (ii) omega-3 oils,

for the manufacture of a medicament for the prevention, delay of progression or the treatment of a disease or condition associated with lipid metabolism and cell proliferation of humans and other species, e.g. metabolic disorders such as obesity, diabetes, anorexia nervosa, bulimia, cachexia, syndrome X, insulin resistance, hypoglycemia, hyperglycemia, hyperuricemia, hyperinsulinemia, hypercholesterolemia, hyperlipidemia, dyslipidemia, mixed dyslipidemia, hypertriglyceridemia, pancreatitis, and nonalcoholic fatty liver disease; cardiovascular diseases, such as atherosclerosis, arteriosclerosis, acute heart failure, congestive heart failure, coronary artery disease, cardiomyopathy, myocardial infarction,

angina pectoris, hypertension, hypotension, stroke, ischemia, ischemic reperfusion injury, aneurysm, restenosis, and vascular stenosis; neoplastic diseases, such as solid tumors, skin cancer, melanoma, lymphoma, and endothelial cancers, for example, breast cancer, lung cancer, colorectal cancer, stomach cancer, other cancers of the gastrointestinal tract (for example, esophageal cancer and pancreatic cancer), prostate cancer, kidney cancer, liver cancer, bladder cancer, cervical cancer, uterine cancer, testicular cancer, and ovarian cancer; dermatological conditions, such as acne vulgaris, more especially hypertriglyceridemia, in particular chylomicronemia (also called hyperchylomicronemia), such as familial chylomicronemia syndrome (FCS) or Type V, Type IV or mutifactorial hyperlipoproteinemia (also known as non-FCS).

As set out before, the DGAT1 inhibitor is preferably selected from (4-{4-[5-(6-Trifluoromethyl-pyridin-3-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid, or a pharmaceutically acceptable salt or ester thereof, and (4-{4-[5-(Benzo[d]oxazol-2-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid or a pharmaceutically acceptable salt or ester thereof.

A further aspect of the present invention is a method for the prevention, delay of progression or the treatment of a disease or condition associated with lipid metabolism and cell proliferation of humans and other species, e.g. metabolic disorders such as obesity, diabetes, anorexia nervosa, bulimia, cachexia, syndrome X, insulin resistance, hypoglycemia, hyperglycemia, hyperuricemia, hyperinsulinemia, hypercholesterolemia, hyperlipidemia, dyslipidemia, mixed dyslipidemia, hypertriglyceridemia, pancreatitis, and nonalcoholic fatty liver disease; cardiovascular diseases, such as atherosclerosis, arteriosclerosis, acute heart failure, congestive heart failure, coronary artery disease, cardiomyopathy, myocardial infarction, angina pectoris, hypertension, hypotension, stroke, ischemia, ischemic reperfusion injury, aneurysm, restenosis, and vascular stenosis; neoplastic diseases, such as solid tumors, skin cancer, melanoma, lymphoma, and endothelial cancers, for example, breast cancer, lung cancer, colorectal cancer, stomach cancer, other cancers of the gastrointestinal tract (for example, esophageal cancer and pancreatic cancer), prostate cancer, kidney cancer, liver cancer, bladder cancer, cervical cancer, uterine cancer, testicular cancer, and ovarian cancer; dermatological conditions, such as acne vulgaris, more especially hypertriglyceridemia, in particular chylomicronemia (also called hyperchylomicronemia), such as familial chylomicronemia syndrome (FCS) or with Type V, Type IV or mutifactorial hyperlipoproteinemia (also known as non-FCS), comprising administering to a warm-blooded animal, e.g. a human in need thereof jointly therapeutically effective amounts of a pharmaceutical combination, such as a combined preparation or pharmaceutical composition, respectively, according to the present invention

comprising at least one DGAT1 inhibitor, or a pharmaceutically acceptable salt or ester thereof and at least one kind of triglyceride lowering drug selected from the group consisting of

(a) at least one PPAR alpha agonist or a pharmaceutically acceptable salt thereof or ester thereof, and
(b) at least one compound selected from the group consisting of
    (i) natural or synthetic omega-3 fatty acids or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof, and
    (ii) omega-3 oils.

As set out before, the DGAT1 inhibitor is preferably selected from (4-{4-[5-(6-Trifluoromethyl-pyridin-3-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid, or a pharmaceutically acceptable salt or ester thereof, and (4-{4-[5-(Benzo[d]oxazol-2-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid or a pharmaceutically acceptable salt or ester thereof.

Preferably, in this method of treating the active ingredients are administered simultaneously or sequentially in any order, separately or in a fixed combination.

A therapeutically effective amount of each of the components of the pharmaceutical combination of the present invention may be administered simultaneously or sequentially and in any order, and the components may be administered separately or as a fixed combination.

For example, the method of treatment of the invention may comprise: administration of at least one DGAT1 inhibitor, or a pharmaceutically acceptable salt or ester thereof – as set out herein before – and at least one kind of triglyceride lowering drug selected from the group consisting of

(a) at least one PPAR alpha agonist or a pharmaceutically acceptable salt thereof or ester thereof, and
(b) at least one compound selected from the group consisting of
    (i) natural or synthetic omega-3 fatty acids or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof, and
    (ii) omega-3 oils,

simultaneously or sequentially in any order, in jointly therapeutically effective amounts, preferably in synergistically effective amounts, e.g. in daily dosages corresponding to the ratios described herein.

The invention further relates to a commercial package comprising jointly therapeutically effective amounts of at least one DGAT1 inhibitor, or a pharmaceutically acceptable salt or ester thereof – as set out herein before – and at least one kind of triglyceride lowering drug selected from the group consisting of

(a) at least one PPAR alpha agonist or a pharmaceutically acceptable salt thereof or ester thereof, and

(b) at least one compound selected from the group consisting of

(i) natural or synthetic omega-3 fatty acids or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof, and

(ii) omega-3 oils,

together with instructions for use thereof in the prevention, delay of progression or the treatment of conditions associated with lipid metabolism and cell proliferation of humans and other species, e.g. metabolic disorders such as obesity, diabetes, anorexia nervosa, bulimia, cachexia, syndrome X, insulin resistance, hypoglycemia, hyperglycemia, hyperuricemia, hyperinsulinemia, hypercholesterolemia, hyperlipidemia, dyslipidemia, mixed dyslipidemia, hypertriglyceridemia, pancreatitis, and nonalcoholic fatty liver disease; cardiovascular diseases, such as atherosclerosis, arteriosclerosis, acute heart failure, congestive heart failure, coronary artery disease, cardiomyopathy, myocardial infarction, angina pectoris, hypertension, hypotension, stroke, ischemia, ischemic reperfusion injury, aneurysm, restenosis, and vascular stenosis; neoplastic diseases, such as solid tumors, skin cancer, melanoma, lymphoma, and endothelial cancers, for example, breast cancer, lung cancer, colorectal cancer, stomach cancer, other cancers of the gastrointestinal tract (for example, esophageal cancer and pancreatic cancer), prostate cancer, kidney cancer, liver cancer, bladder cancer, cervical cancer, uterine cancer, testicular cancer, and ovarian cancer; dermatological conditions, such as acne vulgaris.

In a particular embodiment the disease or condition associated with lipid metabolism and cell proliferation is hypertriglyceridemia, in particular chylomicronemia (also called hyperchylomicronemia), such as familial chylomicronemia syndrome (FCS) or Type V, Type IV or mutifactorial hyperlipoproteinemia (also known as non-FCS).

The present invention furthermore concerns a pharmaceutical combination according to the present invention for use as a medicament.

The present invention furthermore concerns the use of at least one DGAT1 inhibitor, or a pharmaceutically acceptable salt thereof or ester thereof selected from trans-4-[4-[5-[[6-(trifluoromethyl)-3-pyridinyl]amino]-2-pyridinyl]phenyl]cyclohexane acetic acid and trans-4-[4-

[5-[[6-(trifluoromethyl)-3-pyridinyl]amino]-2-pyridinyl]phenyl]cyclohexane acetic acid, sodium salt in combination with at least one kind of drug selected from the group consisting of

(a) at least one fibrate or a pharmaceutically acceptable salt thereof or ester thereof selected from thegroup consisting of fenofibrate, micronized fenofibrate, fenofibric acid, bezafibrate, gemfibrozil, clofibrate and ciprofibrate and

(b) at least one compound selected from the group consisting of

(i) natural or synthetic omega-3 fatty acids or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixture thereof, or

(ii) omega-3 oils, in particular omega-3 oils comprising at least 90 percent (w/w) omega-3 ethyl esters with about 46.5 percent EPA and about 37.5 percent DHA (e.g., OMACOR^{TM})

for the manufacture of a medicament for the prevention, delay of progression or the treatment of a disease or condition associated with lipid metabolism and cell proliferation of humans and other species, e.g. metabolic disorders such as obesity, diabetes, anorexia nervosa, bulimia, cachexia, syndrome X, insulin resistance, hypoglycemia, hyperglycemia, hyperuricemia, hyperinsulinemia, hypercholesterolemia, hyperlipidemia, dyslipidemia, mixed dyslipidemia, hypertriglyceridemia, pancreatitis, and nonalcoholic fatty liver disease; cardiovascular diseases, such as atherosclerosis, arteriosclerosis, acute heart failure, congestive heart failure, coronary artery disease, cardiomyopathy, myocardial infarction, angina pectoris, hypertension, hypotension, stroke, ischemia, ischemic reperfusion injury, aneurysm, restenosis, and vascular stenosis; neoplastic diseases, such as solid tumors, skin cancer, melanoma, lymphoma, and endothelial cancers, for example, breast cancer, lung cancer, colorectal cancer, stomach cancer, other cancers of the gastrointestinal tract (for example, esophageal cancer and pancreatic cancer), prostate cancer, kidney cancer, liver cancer, bladder cancer, cervical cancer, uterine cancer, testicular cancer, and ovarian cancer; dermatological conditions, such as acne vulgaris.

In a particular embodiment the disease or condition associated with lipid metabolism and cell proliferation is hypertriglyceridemia, in particular chylomicronemia (also called hyperchylomicronemia), such as familial chylomicronemia syndrome (FCS) or Type V, Type IV or mutifactorial hyperlipoproteinemia (also known as non-FCS).

The dosage range of the pharmaceutical combination according to the present invention to be employed depends upon factors known to the person skilled in the art including species of the warm-blooded animal, body weight and age, the nature and severity of the condition to be treated, the mode of administration and the particular substance to be employed.

Examples of suitable dosages are provided in more detail above, e.g. in the sections describing the individual components.

The weight ratio of the daily doses of DGAT1 inhibitor, or a pharmaceutically acceptable salt or thereof or ester thereof to at least one kind of triglyceride lowering drug selected from the group consisting of

(a) at least one PPAR alpha agonist or a pharmaceutically acceptable salt thereof or ester thereof, and
(b) at least one compound selected from the group consisting of
    (i) natural or synthetic omega-3 fatty acids or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof, and
    (ii) omega-3 oils.

may vary within wide limits depending, in particular, on the needs of the warm-blooded animal, e.g. human, treated.

Although the present invention has been described in considerable detail with reference to certain preferred versions thereof, other versions are possible without departing from the spirit and scope of the preferred versions contained herein. All references and Patents (U.S. and others) referred to herein are hereby incorporated by reference in their entirety as if set forth in full herein.

The effectiveness of the combination of the present invention can be shown by a number of well-established tests/ models, including but not limited to an open-label clinical study in patients with hypertriglyceridemia. A non-limiting example of a suitable placebo-controlled, double-blind clinical study in patients with hypertriglyceridemia is provided below (Example 3).

The following Examples illustrate the invention described above; they are not, however, intended to limit the scope of the invention in any way. The beneficial effects of the combination of the present invention can also be determined by other test models known as such to the person skilled in the pertinent art.

Examples

Example 1: Tablet comprising a DGAT1 inhibitor.

Compound 1: trans-(4-{4-[5-(6-Trifluoromethyl-pyridin-3-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid, sodium salt

Uncoated tablet comprising a DGAT1 inhibitor, 5 mg of active ingredient, based on free acid of Compound 1:

Ingredients	**mg/tab**
trans-(4-{4-[5-(6-Trifluoromethyl-pyridin-3-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid, sodium salt	5.26
Microcrystalline Cellulose	86.24
Crospovidone	7.0
Colloidal silicon dioxide	0.5
Magnesium Stearate	1.0
Total weight	100

Uncoated tablet comprising a DGAT1 inhibitor, 10 mg of active ingredient, based on free acid of Compound 1:

Ingredients	**mg/tab**
trans-(4-{4-[5-(6-Trifluoromethyl-pyridin-3-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid, sodium salt	10.51
Microcrystalline Cellulose	172.49
Crospovidone	14.0
Colloidal silicon dioxide	1.0
Magnesium Stearate	2.0
Total weight	200

Preparation process

trans-(4-{4-[5-(6-Trifluoromethyl-pyridin-3-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid, sodium salt along with Microcrystalline Cellulose (partial), and Crospovidone (intragranular) are mixed in a low shear mixer. The mixed contents, along with remaining Microcrystalline Cellulose are passed through an oscillating mill equipped with a suitable screen. The screened contents are mixed in a low shear mixer for a suitable amount of time. Colloidal silicon dioxide, screened through an appropriate screen is mixed with the blend from earlier step and the contents are mixed for a suitable amount of time. Magnesium Stearate, screened through a suitable screen size is added to the preblend and mixed for a suitable amount of time. The lubricated intragranular preblend is passed through a roller compaction system for densification at the optimized parameters for feed rate, roll speed and roll force. The ribbons from the process are collected and passed through an oscillating mill equipped with a suitable screen to get the desired milled material. The milled material is then mixed with extragranular prescreened Crospovidone and mixed in a low shear mixer for a suitable amount of time. To the mixture, prescreened Magnesium Stearate is added and mixed for a suitable amount of time. The final blend is then compressed to the desired tablet weight to achieve the optimized thickness, hardness and disintegration time.

Example 2: Animal model to assess the efficacy of a combination of Compound 1 **and a triglyceride lowering drug compound**

Compound 1: trans-(4-{4-[5-(6-Trifluoromethyl-pyridin-3-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid, sodium salt
Triglyceride lowering drug: the PPAR alpha antagonist fenofibrate
The animal model: A chronic study in mice treated with a western diet.

Procedure:
Age-matched male C57Bl/6 mice were acclimated to a Western-type diet (D12079B Research Diets) for two weeks. Mice were then randomized by body weight (n=10/group) to the following treatment arms:

1) Western diet (WD) only;
2) Western diet (WD) containing 1 g of Compound 1 per kg of diet;
3) Western diet (WD) containing 0.5 g fenofibrate per kg of diet;
4) Western diet (WD) containing 1 g of Compound 1 and 0.5 g fenofibrate per kg of diet.

Cumulative food intake and body weight were measured before compound treatment on day 0 and over the course of the treatment. Fasting body composition was measured on day 0 and on day 28. On day 21 overnight fasted mice were challenged with 5 ml corn oil per kg body weight by oral gavage. Plasma triglycerides were measured at 0, 1, 2, and 4 h post corn oil administration.

Triglycerides Analysis: Plasma triglycerides were quantified using a low-volume 384-well assay based on Wako triglyceride reagents (R1, cat# 461-08992; R2, cat# 461-09092; standard, cat# 464-01601; controls, cat#'s 00102 & 00202). In a 384 well "sample plate" (Greiner, cat# 781280), samples were diluted 1:3 in distilled water and mixed thoroughly in preparation of the assay. Five microliters of diluted sample, standard, or control were added to 70 microliter of R1 reagent and incubated for 5 minutes at room temperature. After the incubation, 20 microliter of R2 was added to the mixture and incubated for an additional 15 minutes at room temperature. Lastly, 100 microliter of the mixture was transferred to a black 384 well clear-bottom "read plate" (Greiner cat# 781096) and absorbance measured at 600nm using a SpectraMax M5 spectrophotometer. The standard curve was fit to a linear equation and sample concentrations determined by extrapolation to the standard curve and corrected for dilution. Accounting for dilution, the range of the assay is 9.9 mg/dL to 324 mg/dL.

Results

1. Total test compound intake during the treatment time:

Treatment	Compound Amount in WD food	Total Average Food Intake (per mouse in 20 days)	Total Average Compound Intake (per mouse in 20 days)
Plain WD Control	Non	57.1 g	Non
Compound 1	1 g/kg	51.9 g	51.9 mg
Fenofibrate	0.5 g/kg	52.7 g	26.4 mg
Compound 1 + Fenofibrate	1 g/kg + 0.5 g/kg	49.8 g	49.8 mg + 24.9 mg

2. Body weight gain

Treatment	Body weight gain (g) (per mouse in 20 days)
Plain WD Control	7.9 ± 0.7
Compound 1	4.9 ± 0.6*#
Fenofibrate	4.9 ± 0.4*#
Compound 1 + Fenofibrate	2.7 ± 0.3*

* $p < 0.05$ versus vehicle; # $p < 0.05$ versus Compound 1 + Fenofibrate
Two way ANOVA test with multiple comparisons.

3. Plasma Triglycerides

Treatment	Plasma Triglycerides (mg/dl) T=0 after lipid challenge	Plasma Triglycerides (mg/dl) T=2 hr after lipid challenge
Plain WD Control	80 ± 10	527 ± 34
Compound 1	60 ± 8	215 ± 17*#
Fenofibrate	39 ± 6	372 ± 39*#
Compound 1 + Fenofibrate	25 ± 5	100 ± 13*

* $p < 0.05$ versus vehicle; # $p < 0.05$ versus Compound 1 + Fenofibrate
Two way ANOVA test with multiple comparisons.

4. Body Composition

Analysis of the fat and lean mass on day 0 and day 28 of the experiment, as well as the comparison of the data on day 0 and day 28 showed that whereas there is no significant change in the lean body mass, the body fat mass changes significantly. Whereas the mice on a Western Diet showed an increase in body fat mass of around 5 g, the mice treated with Compound 1 or with fenofibrate only gained about 1 g or less of body fat. Mice treated with the combination of Compound 1 and fenofibrate actually showed a reduction of body fat mass of around 2 g.

Conclusion from the rodent model

The rodent model showed that a combination therapy with Compound 1 and fenofibrate has an additive effect on the suppression of body weight gain and also suppresses postprandial triglycerides in an additive manner. Whereas the combined effect in the mice during the treatment regimen of about 3 to 4 weeks was merely additive the achieved effect with the combination was nevertheless statistically significant and showed a clear advantageous effect. In particular the effect on the lowering of postprandial triglycerides was unexpected.

Extrapolation of the obtained results from a DGAT1 inhibitor and fenofibrate combination to a combination comprising omega-3 fatty acids or omega-3 oils, e.g. fish oils:

The results of Example 2 in mice fed on a high fat diet demonstrate that the two drug, i.e. Compound 1, a DGAT1 inhibitor, and fenofibrate, a PPAR alpha agonist, work together to at least additively reduce body weight gain and plasma triglycerides in response to an oral lipid challenge. Since fenofibrate is an effective PPAR alpha agonist, the results imply that the combination of a DGAT-1 inhibitor and a PPAR alpha agonist are together able to mediate the observed effects. Omega-3 oils or fish oils (such as DHA and EPA), like fenofibrate, are agonists of PPAR alpha as set out above (Keller et al 1993, PNAS, 90, p. 2160, and Larter et al, 2008, J. Gastroenterol. Hepatol. 23, p. 267). It is also known that fish oils mediate some of their effects, like increased beta oxidation of fatty acids (. Ren et al. 1997 J Bio Chem 272(43), p. 26827-32), or increase lipoprotein lipase enzyme activity, the enzyme critical for triglyceride clearance (Rudkowska et al 2010 Molecular Nutrition and Food Research 54(4), p. 543-50) in a PPAR alpha-dependent manner. Based on the observed additive effects of Compound 1, a DGAT1 inhibitor, with fenofibrate in the rodent model, it is reasonable to predict that a DGAT1 inhibitor combined with fish oil could produce similar additive effects through a PPAR alpha-mediated pathway.

Example 3: Study to assess the efficacy and safety of adding Compound 1 alone and in combination with Lovaza® or fenofibrate in patients with severe hypertriglyceridemia.

Compound 1: trans-(4-{4-[5-(6-Trifluoromethyl-pyridin-3-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid, sodium salt

This is a multicenter, randomized, active comparator, placebo-controlled, double-blind pilot study to assess the efficacy and safety of Compound 1 alone and in combination with fenfibrate or Lovaza® in patients with severe hypertriglyceridemia.

The purpose of this study is to determine a dose response signal for Compound 1 monotherapy and to assess the efficacy and safety of adding Compound 1 20 mg to Lovaza® 4 gm or fenofibrate 145 mg.

Study Design

Epoch I (Screening/Wash-out of prior medications): At the first visit, patients are assessed for eligibility to participate in the trial. Patients' entry into the study are determined when all the screening procedures including all inclusion and exclusion criteria are finally assessed. Patient eligibility for participation are assessed according to history of triglyceride levels (> 10 mmol/l or 890 mg/dL) and/or lactescent plasma in addition to the remaining inclusion and exclusion criteria listed below. All eligible patients on prohibited medication (including fenofibrates and/or Lovaza®) are washed out for 8 weeks prior to entry into the dietary lead-in period.

Eligible untreated patients may enter directly into the dietary lead-in once all necessary screening assessments are completed.

Epoch II (Dietary Lead-in Period): Upon completion of washout of prior medications, if applicable, patients enter into a 4-week dietary lead-in period (Week -4). During this period, patients are asked to follow an American Heart Association (AHA) diet (or local country equivalent, if applicable). Patients are asked to return to the clinic 3 weeks later (Day -7) to assess their plasma triglycerides (TG ≥750 mg/dL) while following the AHA diet. If the TG level at Day -7 is less than required (TG ≥750 mg/dL), the lead-in period may be extended for another 7 days and the TG assessment repeated if it is thought to be likely that the patient will qualify.

Epoch III (Treatment Period 1): At Day 0 (randomization), patients who have successfully completed the dietary lead-in period and met the fasting plasma triglycerides criteria (TG ≥ 750 mg/dL (8.5 mmol/L)) and all other entry criteria are randomized in the study in a 1:1:1:1:1:1 ratio.

All patients remain on their AHA diet (or country equivalent) for the duration of the study. After randomization there are 6 weeks of double-blind treatment with:

- Compound 1 5 mg qd or
- Compound 1 20 mg qd or
- Compound 1 40 mg qd or
- Fenofibrate 145 mg qd or
- Lovaza® 4 gm qd or
- Placebo

Epoch IV (Treatment Period 2): At Visit 204 (Week 6), patients randomized to either fenofibrate (Tricor 145) or Lovaza® 4 gm will also receive Compound 1 20 mg in a double-blinded manner. The blind will be maintained by adding Compound 1 20 mg or placebo in all patients. The treatment assignments for the remaining 6 weeks of the study will then be:

- Compound 1 5 mg qd or
- Compound 1 20 mg qd or
- Compound 1 40 mg qd or
- Fenofibrate 145 mg qd + Compound 1 20 mg qd or
- Lovaza® 4 gm qd + Compound 1 20 mg qd or
- Placebo

All patients will remain on their assigned doses of study medication for an additional 6 weeks. The final study visit will be conducted at approximately Week 12. Endpoint fasting TG levels will be measured at week 12.

Population

The study population consist of a representative group of approximately 60 males and females (non-fertile) with plasma TG >750 mg/dL after 3-4 weeks on an AHA diet

Inclusion criteria comprise:

- Male and female subjects ages >18 years of age, inclusive.
- History of plasma TG concentration ≥890 mg/dl (10 mmol/L) or history of lactescent plasma in the fasting state.
- Fasting TG ≥ 750 mg/dL (8.5 mmol/L) at day -7 or repeat of day -7 one week later for those failing to qualify initially and thought likely to qualify on repeat examination prior to randomization.

Exclusion criteria comprise:

- Treatment with Omega-3 fatty acids or niacin or fibrates within 8 weeks of screening.
- Patients with confirmed Familial Chylomicronemia Syndrome (FCS) with hyperlipoproteinemia (HLP) Type-I diagnosis or known to be homozygotes or compound heterozygotes for mutations in HLP Type I-causing genes (such as LPL, apoCII, CPIHBP1, or LMF1) prior to screening.
- Pancreatitis within 3 months prior to screening.
- Uncontrolled type 2 diabetes (T2DM) (as defined by an HbA1c value of ≥8.0% at screening)

- Inflammatory bowel disease, Crohn's disease or ulcerative colitis, any GI surgery within 12 weeks of screening
- BMI > 40 or history of bariatric surgery.
- Nephrotic syndrome, Type 1 diabetes, HIV, HCV or HBV positive.
- Estimated Glomerular Filtration Rate (eGFR) < 60 ml/min/1.73m2

Objectives

The primary objective of this study is to evaluate a dose response signal of 3 dose regiments of Compound 1 (5 mg, 20 mg, 40 mg) in patients at risk for non-FCS chylomicronemia as measured by change from baseline in triglycerides (TG) relative to placebo at 6 weeks.

Secondary objects of this study include:

- To evaluate changes in triglycerides after adding Compound 1 20 mg to background therapy of fenofibrate 145 mg or Lovaza® 4 gm
- To evaluate triglyceride changes from baseline after treatment with Compound 1 monotherapy (5 mg, 20 mg, 40 mg) relative to fenofibrate 145 mg or Lovaza® 4 gm at 6 weeks
- To evaluate triglyceride changes from baseline after treatment with Compound 1 monotherapy (5 mg, 20 mg, 40 mg) relative to placebo at 12 weeks.
- To evaluate triglyceride changes from baseline after treatment with Compound 1 monotherapy (5 mg, 20 mg, 40 mg) relative to the combination of Compound 1 20 mg with fenofibrate 145 mg and Compound 1 20 mg with Lovaza® 4 gm at 12 weeks.
- To assess the safety and tolerability of Compound 1 monotherapy (5 mg, 20 mg, 40 mg) relative to placebo.
- To assess the safety and tolerability of Compound 1 20 mg added to background therapy of fenofibrate 145 mg or Lovaza® 4 gm relative to Compound 1 20 mg monotherapy and placebo.
- To determine change in lipids and lipoprotein profiles in the Compound 1 monotherapy doses as well as when Compound 1 20 mg is added to background therapy of either fenofibrate 145 mg or Lovaza® 4 gm.
- To characterize the pharmacokinetics of Compound 1 alone and in combination with fenofibrate 145 mg or Lovaza® 4 gm.

CLAIMS:

1. A pharmaceutical combinationcomprising

at least one DGAT1 inhibitor selected from (4-{4-[5-(6-Trifluoromethyl-pyridin-3-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid, or a pharmaceutically acceptable salt or ester thereof, and (4-{4-[5-(Benzo[d]oxazol-2-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid or a pharmaceutically acceptable salt or ester thereof,

at least one kind of triglyceride lowering drug selected from the group consisting of

(a) at least one PPAR alpha agonist or a pharmaceutically acceptable salt thereof or ester thereof, and

(b) at least one compound selected from the group consisting of

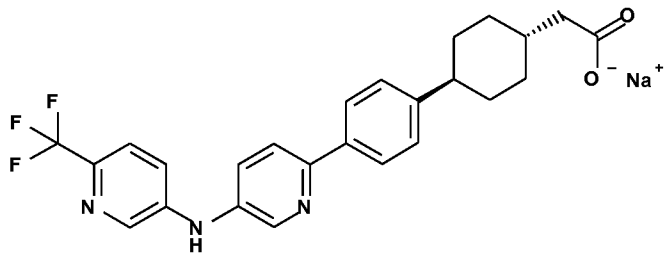
(i) natural or synthetic omega-3 fatty acids or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof, and

(ii) omega-3 oils,

and optionally at least one pharmaceutically acceptable carrier.

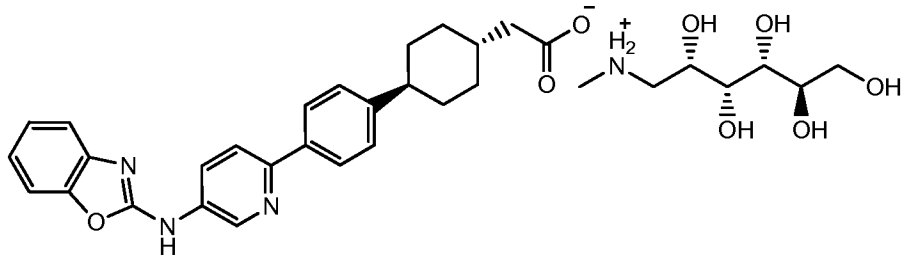
2. A pharmaceutical combination according to claim 1 wherein the DGAT1 inhibitor (4-{4-[5-(6-Trifluoromethyl-pyridin-3-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid is trans-4-[4-[5-[[6-(Trifluoromethyl)-3-pyridinyl]amino]-2-pyridinyl]phenyl] cyclohexane acetic acid, or a pharmaceutically acceptable salt or ester thereof.

3. A pharmaceutical combination according to claim 2 wherein the DGAT1 inhibitor is trans-4-[4-[5-[[6-(trifluoromethyl)-3-pyridinyl]amino]-2-pyridinyl]phenyl] cyclohexane acetic acid sodium salt of the following formula



4. A pharmaceutical combination according to claim 1 wherein the DGAT1 inhibitor (4-{4-[5-(Benzo[d]oxazol-2-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid or a pharmaceutically acceptable salt or ester thereof, is 2-((1R,4R)-4-(4-(5-(benzo[d]oxazol-2-ylamino)pyridin-2-yl)phenyl)cyclohexyl)acetic acid or a salt or ester thereof.

5. A pharmaceutical combination according to claim 4 wherein the DGAT1 inhibitor is 2-((1R,4R)-4-(4-(5-(benzo[d]oxazol-2-ylamino)pyridin-2-yl)phenyl)cyclohexyl)acetic acid meglumine salt of the following formula:



6. A pharmaceutical combination according to any of the claims 1 to 5 wherein the triglyceride lowering drug is a PPAR alpha agonist or a pharmaceutically acceptable salt thereof or ester thereof.

7. A pharmaceutical combination according to claim 6, wherein the PPAR alpha agonist is a fibrate.

8. A pharmaceutical combination according to claim 8, wherein the fibrate is selected from the group consisting of clofibrate, gemfibrozil, fenofibrate, micronized fenofibrate, fenofibric acid, ciprofibrate and bezafibrate.

9. A pharmaceutical combination according to claim 9, wherein the fibrate is fenofibrate.

10. A pharmaceutical combination according to any of the claims 1 to 5 wherein the triglyceride lowering drug is at least one compound selected from the group consisting of
    (i) natural or synthetic omega-3 fatty acids or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof , or
    (ii) omega-3 oils.

11. A pharmaceutical combination according to claim 10, wherein the omega-3 fatty acid or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof, is EPA or DHA or mixtures thereof.

12. A pharmaceutical combination according to claim 10, wherein the omega-3 oil comprises a mixture of omega-3 acids or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof.

13. A pharmaceutical combination according to claim 12, wherein the omega-3 oil comprises EPA and DHA or mixtures thereof.

14. A pharmaceutical combination according to claim 12 or 13, wherein the omega-3 oil in addition comprises other omega-3 oils.

15. A pharmaceutical combination according to any one of claim 10 to 14, wherein the omega-3 oil comprises omega-3 acid ethyl ester.

16. A pharmaceutical combination according to any one of claims 11 to 14, wherein the ratio EPA:DHA is from 99:1 to 1:99, preferably from 2:1 to 1:2.

17. A pharmaceutical combination according to any one of claims 10 to 14, wherein said omega-3 oil comprises at least 90 percent (w/w) omega-3 ethyl esters of which are about 46.5 percent EPA and about 37.5 percent DHA.

18. A pharmaceutical combination according to any one of claims 1 to 17 in the form of a combined preparation for simultaneous, separate or sequential use.

19. A pharmaceutical combination according to any one of claims 1 to 17 in the form of a pharmaceutical composition being a fixed dose combination.

20. A pharmaceutical combination according to any one of the preceding claims 1 to 19 for the use as a medicament.

21. A pharmaceutical combination according to any one of claims 1 to 19 for use in the prevention, delay of progression or treatment of a disease or condition associated with lipid metabolism and cell proliferation of humans and other species, e.g. metabolic disorders such as obesity, diabetes, anorexia nervosa, bulimia, cachexia, syndrome X, insulin resistance, hypoglycemia, hyperglycemia, hyperuricemia, hyperinsulinemia, hypercholesterolemia, hyperlipidemia, dyslipidemia, mixed dyslipidemia, hypertriglyceridemia, pancreatitis, and nonalcoholic fatty liver disease; cardiovascular diseases, such as atherosclerosis, arteriosclerosis, acute heart failure, congestive heart failure, coronary artery disease, cardiomyopathy, myocardial infarction, angina pectoris, hypertension, hypotension, stroke, ischemia, ischemic reperfusion injury, aneurysm, restenosis, and vascular stenosis; neoplastic diseases, such as solid tumors, skin

cancer, melanoma, lymphoma, and endothelial cancers, for example, breast cancer, lung cancer, colorectal cancer, stomach cancer, other cancers of the gastrointestinal tract (for example, esophageal cancer and pancreatic cancer), prostate cancer, kidney cancer, liver cancer, bladder cancer, cervical cancer, uterine cancer, testicular cancer, and ovarian cancer; dermatological conditions, such as acne vulgaris, more especially hypertriglyceridemia, in particular chylomicronemia (also called hyperchylomicronemia), such as familial chylomicronemia syndrome (FCS) or with Type V, Type IV or mutifactorial hyperlipoproteinemia (also known as non-FCS).

22. A pharmaceutical combination according to any one of claims 1 to 19 for use in the prevention, delay of progression or treatment of hypertriglyceridemia, in particular chylomicronemia (also called hyperchylomicronemia), such as familial chylomicronemia syndrome (FCS) or Type V, Type IV or mutifactorial hyperlipoproteinemia (also known as non-FCS).

23. A method for the prevention, delay of progression or treatment of a disease or condition associated with lipid metabolism and cell proliferation of humans and other species, e.g. metabolic disorders such as obesity, diabetes, anorexia nervosa, bulimia, cachexia, syndrome X, insulin resistance, hypoglycemia, hyperglycemia, hyperuricemia, hyperinsulinemia, hypercholesterolemia, hyperlipidemia, dyslipidemia, mixed dyslipidemia, hypertriglyceridemia, pancreatitis, and nonalcoholic fatty liver disease; cardiovascular diseases, such as atherosclerosis, arteriosclerosis, acute heart failure, congestive heart failure, coronary artery disease, cardiomyopathy, myocardial infarction, angina pectoris, hypertension, hypotension, stroke, ischemia, ischemic reperfusion injury, aneurysm, restenosis, and vascular stenosis; neoplastic diseases, such as solid tumors, skin cancer, melanoma, lymphoma, and endothelial cancers, for example, breast cancer, lung cancer, colorectal cancer, stomach cancer, other cancers of the gastrointestinal tract (for example, esophageal cancer and pancreatic cancer), prostate cancer, kidney cancer, liver cancer, bladder cancer, cervical cancer, uterine cancer, testicular cancer, and ovarian cancer; dermatological conditions, such as acne vulgaris, more especially hypertriglyceridemia, in particular chylomicronemia (also called hyperchylomicronemia), such as familial chylomicronemia syndrome (FCS) or with Type V, Type IV or mutifactorial hyperlipoproteinemia (also known as non-FCS), comprising administering to a warm-blooded animal in need thereof jointly therapeutically effective amounts of a pharmaceutical combination as defined in any of claims 1 to 19.

24. A kit of parts comprising at least one DGAT1 inhibitor as defined in any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof or ester thereof and at least one kind of triglyceride lowering drug selected from the group consisting of

    (a) at least one PPAR alpha agonist or a pharmaceutically acceptable salt or ester thereof as defined in any one of claims 7 to 9, and

    (b) at least one compound selected from the group consisting of

        (i) natural or synthetic omega-3 fatty acids or pharmaceutical acceptable esters, derivatives, conjugates, precursors or salts thereof or mixtures thereof as defined in any one of claims 11 to 17, and

        (ii) omega-3 oils as defined in any one of claims 11 to 17,

    in the form of two or three or more separate units of the components.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/039697

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/444 A61K31/4439 A61K31/192 A61K31/202 A61K31/216
A61K31/195 A61P3/00 A61P9/00 A61P35/00 A61P3/04
A61P3/06 A61P3/08 A61P3/10

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)
EPO-Internal, WPI Data, BIOSIS, EMBASE, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/047948 A1 (NOVARTIS AG [CH]; SUTTON PAUL ALLEN [US]; GIRGIS MICHAEL J [US]; LIANG) 12 April 2012 (2012-04-12)	1-3,6-9, 18-24
Y	page 3, line 25 - line 30 page 63; claim 1 page 21, lines 20-27 - page 22, lines 1-13 page 24, line 5 page 22, line 16 - line 25	10-17

X	US 2009/247534 A1 (SERRANO-WU MICHAEL H [US] ET AL) 1 October 2009 (2009-10-01)	1,4-9, 18-23
Y	page 40; examples 5-1 page 45; examples 5-23 page 3, paragraph 91 page 23, left-hand column, last paragraph page 23, paragraph 781	10-17

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[X] Further documents are listed in the continuation of Box C.

[X] 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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

"P" document published prior to the international filing date but later than the priority date claimed

"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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 July 2013	18/07/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Opravz, Petra

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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