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(54) **FORMULATIONS FOR TREATMENT OF LIPOPROTEIN ABNORMALITIES COMPRISING A STATIN AND A METHYLNICOTINAMIDE DERIVATIVE**

FORMULIERUNGEN ZUR BEHANDLUNG VON LIPOPROTEIN- ANORMALITÄTEN MIT EINEM STATIN- UND EINEM METHYLNICOTINAMID-DERIVAT

FORMULATIONS POUR LE TRAITEMENT DES ANORMALITES LIEES AUX LIPOPROTEINES COMPRENANT UNE STATINE ET UN DERIVE DE LA METHYLNICOTINAMIDE

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- **GEBICKI J ET AL: "PRELIMINARY COMMUNICATION 1-METHYLNICOTINAMIDE: A POTENT ANTI-INFLAMMATORY AGENT OF VITAMIN ORIGIN" POLISH JOURNAL OF PHARMACOLOGY, INSTITUTE OF PHARMACOLOGY, KRAKOW,, PL, vol. 55, no. 1, 2003, pages 109-112, XP008048213 ISSN: 1230-6002**

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(Cont. next page)

- **"Trigonella foenum-graecum" GLOBINMED-GLOBAL INFORMATION HUB ON INTEGRATED MEDICINE, [Online] 2003, pages 1-8, XP002445860 Retrieved from the Internet: URL: http://210.19.20.8/NHIContent/safetyDetail.aspx?id=SAF00013#00000102> [retrieved on 2007-08-07]**

Description

Technical field

[0001] The present invention relates to a combination of a statin and a nicotinamide derivative that can be used in therapy, in particular for treating dyslipidemia or atherosclerosis.

Background of the Invention

[0002] It has been clear for several decades that high total cholesterol, high triglyceride, low high-density lipoprotein cholesterol, normal to elevated low-density lipoprotein cholesterol, or small low-density lipoprotein particles are related to a variety of diseases, conditions and disorders.

[0003] The evidence linking elevated serum cholesterol to coronary heart disease is overwhelming. (Badimon et at, Circulation, 86 Suppl. III, 1992, 86-94). Circulating cholesterol is carried by plasma lipoproteins, which are complex particles of lipid and protein that transport lipids in the blood. Low density lipoprotein (LDL) and high density lipoprotein (HDL) are the major cholesterol-carrier proteins. LDL is believed to be responsible for the delivery of cholesterol from the liver, where it is synthesized or obtained from dietary sources, to extrahepatic tissues in the body. The term "reverse cholesterol transport" describes the transport of cholesterol from extrahepatic tissues to the liver, where it is catabolized and eliminated. It is believed that plasma HDL particles play a major role in the reverse transport process, acting as scavengers of tissue cholesterol. Id. HDL is also responsible for the removal non- cholesterol lipid, oxidized cholesterol and other oxidized products from the bloodstream. Atherosclerosis, for example, is a slowly progressive disease, characterized by the accumulation of cholesterol within the arterial wall. Compelling evidence supports the belief that lipids deposited in atherosclerotic lesions are derived primarily from plasma apolipoprotein B (apo B)-containing lipoproteins, which include chylomicrons, CLDL, IDL and LDL. See Badimon et al, 1992, Circulation 86:(Suppl. 111)86-94. The apoB-containing lipoprotein, and in particular LDL, has popularly become known as the "bad" cholesterol. In contrast, HDL serum levels correlate inversely with coronary heart disease. Indeed, high serum levels of HDL is regarded as a negative risk factor. It is hypothesized that a high level of plasma HDL is not only protective against coronary artery disease, but may actually induce regression of atherosclerotic plaque. See Dansky and Fisher, 1999, Circulation 100: 1762-3. Thus, HDL has popularly become known as the "good" cholesterol.

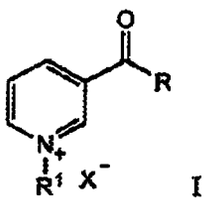
[0004] Further, dyslipidemia is caused by various factors including, but not limited to, high total cholesterol, high triglycerides, low high-density lipoprotein cholesterol, normal to elevated low-density lipoprotein cholesterol, or small low-density lipoprotein particles.

[0005] US-A-5,260,305 and WO99/06046 disclose that nicotinic acid or related acid derivatives thereof can be used together with statins for treating hyperlipidemia, reducing serum cholesterol level, and inhibiting or treating atherosclerosis.

[0006] Thus, there is a continued need to find new therapeutic agents to treat dyslipidemia. Accordingly, there is a great need to develop compounds and pharmaceutical compositions that will raise HDL levels, lower LDL levels, and/or lower triglyceride levels in a subject.

Summary of the invention

[0007] Accordingly, in one aspect, the invention provides a pharmaceutical composition comprising a statin and a 1-methylnicotinamide salt of Formula 1:



I

wherein R represents NH_2; R^1 represents methyl; and X^- is a physiologically suitable counter-anion.

[0008] In particular, the salt is chloride, benzoate, salicylate, acetate, citrate or lactate.

[0009] Preferably, the salt of Formula I is 1-methylnicotinamide chloride, 1-methylnicotinamide citrate or 1-methylnicotinamide lactate.

[0010] In one embodiment, the statin is mevastatin, lovastatin, simvastatin, pravastatin, fluvastatin, pitavastatin, atorvastatin, cerivastatin, rosuvastatin, or pentostatin, or a pharmaceutically acceptable salt, solvate, clathrate, polymorph,

prodrug, or pharmacologically active metabolite thereof.

[0011] In another aspect, the invention provides a combination comprising a statin and a 1-methylnicotinamide salt of Formula I as defined above for use in therapy.

[0012] In another aspect, the invention provides a use of a combination comprising a statin and a 1-methylnicotinamide salt of Formula I as defined above for preparing a pharmaceutical composition for treating dyslipidemia or atherosclerosis.

[0013] In another aspect, the invention provides a combination comprising a statin and a 1-methylnicotinamide salt of Formula I as defined above for use in the treatment of dyslipidemia or atherosclerosis.

[0014] In an embodiment, the statin and the salt of Formula I are co-administered to the subject. In another embodiment, the statin and the salt of Formula I are administered sequentially to the subject. In another embodiment, the statin and the salt of Formula I are administered orally, nasally, rectally, intravaginally, parenterally, buccally, sublingually or topically.

[0015] In another embodiment, the statin and the salt of Formula I are formulated using one or more pharmaceutically acceptable excipients chosen from starch, sugar, cellulose, diluent, granulating agent, lubricant, binder, disintegrating agent, wetting agent, emulsifier, coloring agent, release agent, coating agent, sweetening agent, flavoring agent, perfuming agent, preservative, antioxidant, plasticizer, gelling agent, thickener, hardener, setting agent, suspending agent, surfactant, humectant, carrier, stabilizer, or a combination thereof. In another embodiment, the statin and the salt of Formula I are each administered from one to five times per day. In another embodiment, the statin and the salt of Formula I are each administered one time per day. In yet another embodiment, the subject is a mammal. In another embodiment, the subject is a human. In another embodiment, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier, diluent or excipient.

[0016] In another embodiment, the invention provides a pharmaceutical composition, together with one or more pharmaceutically acceptable carriers, diluents or excipients. In another embodiment, the invention provides pharmaceutical composition wherein the pharmaceutical composition is in tablet form. In yet another embodiment, the pharmaceutical composition is in capsule form. In another embodiment, the pharmaceutical composition is in controlled release or sustained release form.

[0017] The composition or combination of the invention can be used for treating atherosclerosis in a subject in need thereof by administering to the subject a pharmaceutical composition comprising a statin and a salt of Formula I. In another embodiment, the composition or combination of the invention can be used for lowering LDL-cholesterol levels in a subject in need thereof by administering to the subject a pharmaceutical composition comprising a statin and a salt of Formula I. In still another embodiment, the composition or combination of the invention can be used for raising HDL-cholesterol levels in a subject in need thereof by administering to the subject a pharmaceutical composition comprising a statin and a salt of Formula I.

[0018] In an embodiment of the invention, the salt of Formula I is administered first followed by administration of the statin. In another embodiment of the invention, the statin is administered first followed by administration of the salt of Formula I. In still another embodiment of the invention, the statin and the salt of Formula I are administered simultaneously.

[0019] In a particular embodiment, dyslipidemia is a low HDL level, a high LDL level or high total cholesterol, or any combination thereof.

[0020] In another embodiment, dyslipidemia is associated with atherosclerosis.

Brief Description of the Drawings

[0021]

Figure 1 demonstrates that MNA lowers triglyceride levels in rats fed a hypertriglyceridemic diet.

Figure 2 demonstrates that MNA slows atherosclerosis progression in apoE/LDLR$^{-/-}$ mice.

Detailed Description of the Invention

[0022] It is well known that nicotinic acid (NAc) in high doses possesses important properties in the correction of lipoprotein profile (i.e. the treatment of lipoprotein abnormalities), mostly by reducing triglyceride (TG) and elevating HDL levels. The main disadvantage of nicotinic acid therapy is associated with its side effects. Very frequently, cutaneous vasolidation and flushing are observed.

[0023] Studies performed by the instant inventors have demonstrated that a pyridinium salt, namely, methylnicotinamide (MNA is a molecule that can be used for the treatment of lipoprotein abnormalities. MNA is bound as a cationic molecule to Sepharose immobilized heparin (see e.g., International Application No. PCT/EP2005/050057). It was found that MNA releases PGI_2 and it is cytoprotective to various cell lines. In addition, MNA is chemically very stable, nontoxic and very well tolerated.

[0024] The statins are a family of compounds that are usually inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis. As HMG-CoA reductase inhibitors, the statins are able to reduce plasma cholesterol levels in various mammalian species, including humans and are therefore effective in the treatment of hypercholesterolaemia.

Definitions

[0025] These and other embodiments of the invention will be described with preference to following definitions that, for convenience, are collected here.

[0026] The terms "dyslipidemia" and "atherosclerosis" as used herein, describe diseases and disorders that may be treated or prevented (or a symptom of such disease or disorder that may be reduced) by the compositions of the intention. In particular, dyslipidemia is caused by either high total cholesterol, high triglycerides, low high- density lipoprotein cholesterol, normal to elevated low-density lipoprotein cholesterol, or small low-density lipoprotein particles in a subject, or any combination thereof. These factors have been shown to play a role in a variety of diseases and disorders, including, but not limited to, a disorder associated with the development and progress of atherosclerosis (e.g., hypertension, diabetes or obesity).

[0027] In a particular embodiment, atherosclerosis is associated with an acute cardiovascular event, in particular sudden cardiac death, acute coronary syndrome (including unstable coronary artery disease, and (myocardial infarct), the necessity of coronary angioplasty, coronary-aortal by-pass surgery (CABG), any type of surgery with extracorporeal circulation, ischemic stoke, or peripheral circulation revascularization.

[0028] In another particular embodiment, atherosclerosis can be treated in patients with chronic coronary disease, ischemic cerebrovascular episode or artherosclerosis of the extremities, including obliterans.

[0029] Particular forms of dyslipidemia are hypercholesterolemia or hypertriglyceridemia.

[0030] In a particular embodiment of the invention, dyslipidemia can be treated by raising HDL levels in a subject, decreasing LDL levels in a subject, lowering triglycerides in a subject, and/or lowering total cholesterol in a subject by administering to the subject in need thereof the composition or combination of the invention.

[0031] The term "treatment" or "treating," as used herein, is defined as the application or administration of a therapeutic agent, i.e., a salt of Formula I in combination with a statin, to a subject, who has dyslipidemia, a symptom of dyslipidemia or a predisposition toward dyslipidemia, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve or affect dyslipidemia or the symptoms of dyslipidemia. Such treatments may be specifically tailored or modified, based on knowledge obtained from the field of pharmacogenomics.

[0032] The term "subject" includes living organisms in which dyslipidemia or artherosclerosis can occur, or which are susceptible to dyslipidemia. The term "subject" includes animals (e.g., mammals, e.g., cats, dogs, horses, pigs, cows, goats, sheep, rodents, e.g., mice or rats, rabbits, squirrels, bears, primates (e.g., chimpanzees, monkeys, gorillas, and humans)), as well as chickens, ducks, geese, and transgenic species thereof. Administration of the compositions of the present invention to a subject to be treated can be carried out using known procedures, at dosages and for periods of time effective to inhibit dyslipidemia in the subject. An effective amount of the therapeutic compound necessary to achieve a therapeutic effect may vary according to factors such as the state of the disease or disorder in the subject, the age, sex, and weight of the subject, and the ability of the therapeutic compound to inhibit the dyslipidemia in the subject. Dosage regimens can be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. A nonlimiting example of an effective dose range for a therapeutic compound of the invention (i.e. MNA) is between 1 and 500 mg/kg of body weight/per day. One of ordinary skill in the art would be able to study the relevant factors and make the determination regarding the effective amount of the therapeutic compound without undue experimentation.

[0033] Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patients, composition, and mode of administration, without being toxic to the patient.

[0034] In particular, the selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

[0035] A medical doctor, e.g., physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds employed in the pharmaceutical composition of the invention at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

[0036] The regimen of administration can affect what constitutes an effective amount. The therapeutic formulations can be administered to the subject either prior to or after the onset of dyslipidemia. Further, several divided dosages, as well as staggered dosages, can be administered daily or sequentially, or the dose can be continuously infuse, or can be a bolus injection. Further, the dosages of the therapeutic formulations can be proportionally increased or decreased as indicated by the exigencies of the therapeutic or prophylactic situation. In particular embodiments, it is especially advantageous to formulate compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit containing a predetermined quantity of therapeutic compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical vehicle. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristic of the therapeutic compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding/formulating such a therapeutic compound for the treatment of dyslipidemia.

[0037] The 1-methylnicotinamide salt used in the invention, which is also referred to herein as simply MNA, can be synthesized using techniques well-known the one skilled in the art of organic synthesis.

[0038] The salt of Formula I in combination with a statin slow the progression of atherosclerotic plaques (e.g., progression of atherosclerotic plaques is slowed in coronary arteries, in carotid arteries, in the peripheral arterial system) or cause the regression of atherosclerotic plaques.

[0039] The salt of Formula I in combination with a statin raise HDL levels in a subject, decrease LDL levels in a subject, lower triglycerides in a subject, and/or lower total cholesterol in a subject.

[0040] Without being bound by theory, it is believed that the salts of Formula I are effective in treating dyslipidemia for the following reasons: on the surface of the vascular endothelium, polyanionic molecules, such as glycosaminoglycans, are present and it would be expected that the molecules able to manifest some endothelial potential should be bound to vascular endothelium. The salts of Formula I, which are positively charged, bind to the negatively charged glycosaminoglycans present on the vascular endothelium surface due to electrostatic interactions. This binding can result in manifestation of various endothelial effects, some of which can be positive from pharmacologic view point, for example release of NO and/or prostacyclin. Further, this activity can result in the treatment or prevention of dyslipidemia or atherosclerosis (which can be caused by, e.g., high total cholesterol, high triglycerides, low high-density lipoprotein cholesterol, normal to elevated low-density lipoprotein cholesterol, or small low-density lipoprotein particles in the subject).

[0041] As used herein, the language "pharmaceutically acceptable salt" refers to a salt of the administered compounds prepared from pharmaceutically acceptable non-toxic acids including inorganic acids, organic acids, solvates, hydrates, or clathrates thereof. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, and phosphoric. Appropriate organic acids may be selected, for example, from aliphatic, aromatic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, camphorsulfonic, citric, fumaric, gluconic, isethionic, lactic, malic, mucic, tartaric, para-toluenesulfonic, glycolic, glucuronic, maleic, furoic, glutamic, benzoic, anthranilic, salicylic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, pantothenic, benzenesulfonic (besylate), stearic, sulfanilic, alginic, galacturonic.

[0042] In a particular embodiment, the salt of Formula I is the chloride, form of 1-methylnicotinamide.

[0043] As described above, the salts of Formula I are co-administered with statins. The term "statin," where used in the specification and the appending claims, is synonymous with the terms "3-hydroxy-3-methylglutary-1-Coenzyme A reductase inhibitor" and "HMG-CoA reductase inhibitor." These three terms are used interchangeably in the art. As the synonyms suggest, statins are inhibitors of 3-hydroxy- 3-methylglutaryl Coenzyme A reductase and, as such, are effective in lowering the level of blood plasma cholesterol. Statins and pharmaceutically acceptable salts thereof are particularly useful in lowering low-density lipoprotein cholesterol levels in mammals, and particularly in humans.

[0044] Statins suitable for use in the compositions and combinations of the invention are also disclosed in U.S. Pat. Nos. 4,681,893; 5,273,995; 5,356,896; 5,354,772; 5,686,104; 5,969,156; and 6,126,971. As some statins may exist in an inactive form, such as a lactone {e.g., simvastatin), the invention encompasses using the active form {e.g., b-hydroxy acid form) of them. See Physicians Desk Reference, 54.sup.th Ed. (2000) pp. 1917-1920.

[0045] Statins include mevastatin, lovastatin, simvastatin, pravastatin, fluvastatin, pitavastatin, atorvastatin, cerivastatin, rosuvastatin, or pentostatin, or a pharmaceutically acceptable salt, solvate, clathrate, polymorph, prodrug, or pharmacologically active metabolite thereof.

[0046] Preferred statins are those agents which have been marketed, most preferred are pravastatin {e.g., Pravachol™), fluvastatin, simvastatin {e.g., Zocor™), lovastatin {e.g., Mevacor™), atorvastatin, or pitavastatin or a pharmaceutically acceptable salt thereof.

[0047] In some embodiments, a salt of Formula I and a statin are included in a single composition, which is administered to a. subject having dyslipidemia or atherosclerosis. In other embodiments, a salt of Formula I and a statin are administered separately to such a subject. The first and at least one second compound may either be co-administered to a subject (i.e., at the same time) or be administered sequentially (i.e., one after the other).

[0048] A combination of compounds described herein can either result in synergistic increase in effectiveness against

dyslipidemia or atherosclerosis, relative to effectiveness following administration of each compound when used alone, or such an increase can be additive. Compositions described herein typically include lower dosages of each compound in a composition, thereby avoiding adverse interactions between compounds and/or harmful side effects, such as ones which have been reported for similar compounds. Furthermore, normal amounts of each compound when given in combination could provide for greater efficacy in subjects who are either unresponsive or minimally responsive to each compound when used alone.

[0049] For example, statins have been associated with some side-effects, including myalgias, muscle cramps, myositis, myopathy, and other gastrointestinal problem. The administration of MNA in combination with a statin to a subject in need thereof may serve to counteract unwanted side-effects associated with statin use.

[0050] A synergistic effect can be calculated, for example, using suitable methods such as, for example, the Sigmoid-Emax equation (Holford, N. H. G. and Scheiner, L. B., Clin. Pharmacokinet. 6: 429-453 (1981)), the equation of Loewe additivity (Loewe, S. and Muischnek, H., Arch. Exp. Pathol Pharmacol. 114: 313-326 (1926)) and the median- effect equation (Chou, T. C. and Talalay, P., Adv. Enzyme Regul. 22: 27-55 (1984)). Each equation referred to above can be applied to experimental data to generate a corresponding graph to aid in assessing the effects of the drug combination. The corresponding graphs associated with the equations referred to above are the concentration-effect curve, isobologram curve and combination index curve, respectively.

[0051] Dosage of salts of Formula I for administration can be in the range of from about 1 ng to about 10,000 mg, about 5 ng to about 9,500 mg, about 10 ng to about 9,000 mg, about 20 ng to about 8,500 mg, about 30 ng to about 7,500 mg, about 40 ng to about 7,000 mg, about 50 ng to about 6,500 mg, about 100 ng to about 6,000 mg, about 200 ng to about 5,500 mg, about 300 ng to about 5,000 mg, about 400 ng to about 4,500 mg, about 500 ng to about 4,000 mg, about 1 μg to about 3,500 mg, about 5 μg to about 3,000 mg, about 10 μg to about 2,600 mg, about 20 μg to about 2,575 mg, about 30 μg to about 2,550 mg, about 40 μg to about 2,500 mg, about 50 μg to about 2,475 mg, about 100 μg to about 2,450 mg, about 200 μg to about 2,425 mg, about 300 μg to about 2,000, about 400 μg to about 1,175 mg, about 500 μg to about 1,150 mg, about 0.5 mg to about 1,125 mg, about 1 mg to about 1,100 mg, about 1.25 mg to about 1,075 mg, about 1.5 mg to about 1,050 mg, about 2.0 mg to about 1,025 mg, about 2.5 mg to about 1,000 mg, about 3.0 mg to about 975 mg, about 3.5 mg to about 950 mg, about 4.0 mg to about 925 mg, about 4.5 mg to about 900 mg, about 5 mg to about 875 mg, about 10 mg to about 850 mg, about 20 mg to about 825 mg, about 30 mg to about 800 mg, about 40 mg to about 775 mg, about 50 mg to about 750 mg, about 100 mg to about 725 mg, about 200 mg to about 700 mg, about 300 mg to about 675 mg, about 400 mg to about 650 mg, about 500 mg, or about 525 mg to about 625 mg. The salt of Formula I is administered in combination with a statin, wherein the statin is administered in a range described above.

[0052] In some embodiments, the dose of a salt of Formula I is between about 0.0001 mg and about 25 mg. In some embodiments of the invention, a dose of a salt of Formula I used in compositions described herein is less than about 100 mg, or less than about 80 mg, or less than about 60 mg, or less than about 50 mg, or less than about 30 mg, or less than about 20 mg, or less than about 10 mg, or less than about 5 mg, or less than about 2 mg, or less than about 0.5 mg. Similarly, in some embodiments, a dose of a second compound (i.e., a statin) as described herein is less than about 1000 mg, or less than about 800 mg, or less than about 600 mg, or less than about 500 mg, or less than about 400 mg, or less than about 300 mg, or less than about 200 mg, or less than about 100 mg, or less than about 50 mg, or less than about 40 mg, or less than about 30 mg, or less than about 25 mg, or less than about 20 mg, or less than about 15 mg, or less than about 10 mg, or less than about 5 mg, or less than about 2 mg, or less than about 1 mg, or less than about 0.5 mg.

Formulations for Administration

[0053] In another embodiment, the present invention is directed to a packaged pharmaceutical composition comprising a container holding a therapeutically effective amount of a salt of Formula I in combination with a statin; and instructions for using the compound to treat, prevent, or reduce one or more symptoms of dyslipidemia or atherosclerosis in a subject.

[0054] The term "container" includes any receptacle for holding the pharmaceutical composition. For example, in one embodiment, the container is the packaging that contains the pharmaceutical composition. In other embodiments, the container is not the packaging that contains the pharmaceutical composition, i.e., the container is a receptacle, such as a box or vial that contains the packaged pharmaceutical composition or unpackaged pharmaceutical composition and the instructions for use of the pharmaceutical composition. Moreover, packaging techniques are well known in the art. It should be understood that the instructions for use of the pharmaceutical composition may be contained on the packaging containing the pharmaceutical composition, and as such the instructions form an increased functional relationship to the packaged product. However, it should be understood that the instructions can contain information pertaining to the compounds ability to perform its intended function, e.g., treating, preventing, or reducing dyslipidemia or atherosclerosis in a subject.

[0055] The language "therapeutically effective amount" describes the amount of the salt of Formula I of the invention

that is effective to treat dyslipidemia or atherosclerosis in a subject.

[0056] The language "pharmaceutically acceptable carrier" includes a pharmaceutically acceptable materials, composition or carriers, such as a liquid or solid filler, diluent, excipients, solvent or encapsulating material, involved in carrying or transporting a compound(s) of the present invention within or to the subject such that it can perform its intended function. Typically, such compounds are carried or transported from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation, and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose, acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil., corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical formulations. As used herein "pharmaceutically acceptable carrier" also includes any and all coating, antibacterial and antifungal agents, and absorption delaying agents, and the like that are compatible with the activity of the compound, and are physiologically acceptable to the subject. Supplementary active compounds can also be incorporated into the compositions.

[0057] The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particles size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, sodium chloride, or polyalcohols such as mannitol and sorbitol, in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the compositions an agent which delays absorption, for example, aluminum monostearate or gelatin. In one embodiment, the pharmaceutically acceptable carrier is not DMSO alone.

[0058] The compounds for use in the invention can be formulated for administration by any suitable route, such as for oral or parenteral, for example, transdermal, transmucosal (e.g., sublingual, lingual, (trans)buccal, (trans)urethral, vaginal (e.g., trans- and perivaginally), (intranasal and (Trans)rectal), intravesical, intrapulmonary, intraduodenal, intrathecal, subcutaneous, intramuscular, intradermal, intra-arterial, intravenous, intrabronchial, inhalation, and topical administration. Suitable compositions and dosage forms include, for example, tablets, capsules, caplets, pills, gel caps, troches, dispersions, suspensions, solutions, syrups, granules, beads, transdermal patches, gels, powders, pellets, magmas, lozenges, creams, pastes, plasters, lotions, discs, suppositories, liquid sprays for nasal or oral administration, dry powder or aerosolized formulations for inhalation, compositions and formulation for intravesical administration and the like. It should be understood that the formulations and compositions that would be useful in the present invention are not limited to the particular formulations and composition that are described herein.

Oral Administration.

[0059] For example, for oral administration the compounds can be in the form of tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., polyvinylpyrrolidone, hydroxypropylcellulose or hydroxypropylmethylcellulose); fillers (e.g., cornstarch, lactose, macrocrystalline cellulose or calcium phosphate), lubricants (e.g., magnesium stearate, talc, or silica); disintegrates (e.g., sodium starch glycollate); or wetting agents (e.g., sodium lauryl sulphate). If desired, the tablets can be coated using suitable methods and coating materials such was OP ADR Y™ film coating systems available from Colorcon, West Point, Pa. (e.g., OPADRY™ OY Type, OY-C Type, Organic Enteric OY-P Type, Aqueous Enteric OY-A Type, OY-PM Type and OPADRY™ White, 32K1 8400). Liquid preparation for oral administration can be in the form of solutions, syrups or suspensions. The liquid preparations can be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agent (e.g., lecithin or acacia); nonaqueous vehicles (e.g., almond oil, oily esters or ethyl alcohol); and preservatives (e.g., ethyl or propyl p-hydroxy benzoates or sorbic acid).

Parenteral Administration

[0060] For parenteral administration, the compounds for use in the invention can be formulated for injection or infusion, tor example, intravenous, intramuscular or subcutaneous injection or infusion, or for administration in a bolus dose and/or continuous infusion. Suspensions, solutions or emulsions in an oily or aqueous vehicle, optionally containing other

formulatory agents such as suspending, stabilizing and/or dispersing agents can be used.

Transmucosal Administration

[0061] Transmucosal administration is carried out using any type of formulation or dosage unit suitable for application to mucosal tissue. For example, the selected active agent can be administered to the buccal mucosal in an adhesive tablet or patch, sublingually administered by placing a solid dosage form under the tongue, lingually administered by placing a solid dosage form on the tongue, administered nasally as droplets or a nasal spray, administered by inhalation of an aerosol formulation, a non- aerosol liquid formulation, or a dry powder, placed within or near the rectum ("transrectal" formulations), or administered to the urethra as a suppository, ointment, or the like.

Transrectal Administration

[0062] Transrectal dosage forms may include rectal suppositories, creams, ointments, any liquid formulations (enemas). The suppository, cream, ointment or liquid formulation for transrectal delivery comprises a therapeutically effective amount of the selected active agent and one or more conventional nontoxic carriers suitable for transrectal drug administration. The transrectal dosage forms of the present invention can be manufactured using conventional processes. The transrectal dosage unit can be fabricated to disintegrate rapidly or over a period of several hours. The time period for complete disintegration may be in the range of from about 10 minutes to about 6 hours, e.g., less than about 3 hours.

Intranasal or Inhalation Administration

[0063] The active agents may also be administered intranasally or by inhalation. Compositions for intranasal administration are generally liquid formulations for administration as a spray or in the form of drops, although powder formulations for intranasal administration, e.g., insufflations, nasal gels, creams, pastes or ointments or other suitable formulators can be used. For liquid formulations, the active agent can be formulated into a solution, e.g., water or isotonic saline, buffered or unbuffered, or as a suspension. In certain embodiments, such solutions or suspensions are isotonic relative to nasal secretions and of about the same pH, ranging e.g., from about pH 4.0 to about pH 7.4 or, from about pH 6.0 to about pH 7.0. Buffers should be physiologically compatible and include, for example, phosphate buffers. Furthermore, various devices are available in the art for the generation of drops, droplets and sprays, including droppers, squeeze bottles, and manually and electrically powered intranasal pump dispensers. Active agent containing intranasal carriers can also include nasal gels, creams, pastes or ointments with a viscosity of e.g., from about 10 to about 6500 cps, or greater, depending on the desired sustained contact with the nasal mucosal surfaces. Such carrier viscous formulations may be based upon, for example, alkylcelluloses and/or other biocompatible carriers of high viscosity well known to the art (see e.g., Remington: The Science and Practice of Pharmacy, supra). Other ingredients, such as preservatives, colorants, lubricating or viscous mineral or vegetable oils, perfumes, natural or synthetic plant extracts such as aromatic oils, and humectants and viscosity enhancers such as, e.g., glycerol, can also be included to provide additional viscosity, moisture retention and a pleasant texture and odor for the formulation. Formulations for inhalation may be prepared as an aerosol, either a solution aerosol in which the active agent is solubilized in a carrier (e.g., propellant) or a dispersion aerosol in which the active agent is suspended or dispersed throughout a carrier and an optional solvent. Non-aerosol formulations for inhalation can take the form of a liquid, typically an aqueous suspension, although aqueous solutions may be used as well. In such a case, the carrier is typically a sodium chloride solution having a concentration such that the formulation is isotonic relative to normal body fluid. In addition to the carriers, the liquid formulations can contain water and/or excipients including an antimicrobial preservative (e.g., benzalkonium chloride, benzethonium chloride, chlorobutanol, phenylethyl alcohol, thimerosal and combinations thereof), a buffering agent (e.g., citric acids, potassium metaphosphate, potassium phosphate, sodium acetate, sodium citrate, and combinations thereof), a surfactant (e.g., polysorbate 80, sodium lauryl sulfate, sorbitan monopalmitate and combinations thereon), and/or a suspending agent (e.g., agar, bentonite, microcrystalline cellulose, sodium carboxymethylcellulose, hydroxypropyl methylcellulose, tragacanth, veegum and combinations thereof). Non-aerosol formulations for inhalation can also comprise dry powder formulations, particularly insufflations in which the powder has an average particles size of from about 0.1 μm to about 50 μm, e.g., from about 1 μm to about 25 μm.

Topical Formulation

[0064] Topical formulations can be in any form suitable for application to the body surface, and may comprise, for example, an ointment, cream, gel, lotion, solution, paste or the like, and/or may be prepared so as to contain liposomes, micelles, and/or microspheres. In certain embodiments, topical formulations herein are ointments, creams and gels.

Transdermal Administration

[0065] The compounds of the invention may also be administered through the skin or mucosal tissue using conventional transdermal drug delivery systems, wherein the agent is contained within a laminated structure (typically referred to as a transdermal "patch") that serves as a drag delivery device to be affixed to the skin. Transdermal drug delivery may involve passive diffusion or it may be facilitated using electrotransport, e.g., iontophoresis. In a typical transdermal "patch," the drug composition is contained in a layer, or "reservoir," underlying an upper blacking layer. The laminated structure may contain a single reservoir, or it may contain multiple reservoirs. In one type of patch, referred to as a "monolithic" system, the reservoir is comprised of a polymeric matrix of a pharmaceutically acceptable contact adhesive material that serves to affix the system to the skin during drug delivery. Examples of suitable skin contact adhesive materials include, but are not limited to, polyethylenes, polysiloxanes, polyisobutylenes, polyacrylates, polyurethanes, and the like. Alternatively, the drug-containing reservoir and skin contact adhesive are separate and distinct layers, with the adhesive underlying the reservoir which, in this case, may be either a polymeric matrix as described above, or it may be a liquid or hydrogel reservoir, or may take some other form.

Additional Administration Forms

[0066] Additional dosage forms of this invention include dosage forms as described in U.S. Pat. No. 6,340,473, U.S. Pat. No. 6,488,962, U.S. Pat. No. 6,451,808, U.S. Pat. No. 5,972,389, U.S. Pat. No. 5,582,837, and U.S. Pat. No. 5,007,790. Additional dosage forms of this invention also include dosages forms as described in U.S. patent application Ser. No. 20030147952, U.S. patent application Ser. No. 20030104062, U.S. patent application Ser. No. 20030104053, U.S. patent application Ser. No. 20030044466, U.S. patent Application Ser. No. 20030039688, and U.S. patent application Ser. No. 20020051820. Additional dosage forms of this invention also include dosage forms as described in PCT Patent Application WO 03/35041, PCT Patent Application WO 03/35040, PCT Patent Application WO 03/35029, PCT Patent Application WO 0/335177, PCT Patent Application WO 03/35039, PCT Patent Application WO 02/96404, PCT Patent Application WO 02/32416, PCT Patent Application WO 01/97783, PCT Patent Application WO 01/56544, PCT Patent Application WO 01/32217, PCT Patent Application WO 98/55107, PCT Patent Application WO 98/11879, PCT Patent Application WO 97/47285, PCT Patent Application WO 93/18755, and PCT Patent Application WO 90/11757.

Controled Release Formulations and Delivery Systems

[0067] In certain embodiments, the formulations of the present invention can be, but are not limited to, short-term, rapid-offset, as well as controlled, for example, sustained release, delayed release and pulsatile release formulations.

[0068] The term sustained release is used in its conventional sense to refer to a drug formulation that provides for gradual release of a drug over an extended period of time, and that may, although not necessarily, result in substantially constant blood levels of a drug over an extended time period. The period of time can be as long as a month or more and should be a release which is longer that the same amount of agent administered in bolus form.

[0069] For sustained release, the compounds can be formulated with a suitable polymer or hydrophobic materials which provides sustained release properties to the compounds. As such, the compounds for use the method of the invention can be administered in the form of microparticles for example, by injection or in the form of wafers or discs by implantation.

[0070] In a preferred embodiment of the invention, the salts of Formula I, are administered to a subject in combination with a statin, using a sustained release formulation. The term delayed release is used herein in its conventional sense to refer to a drug formulation that provides for an initial release of the drug after some delay following drug administration and that mat, although not necessarily, includes a delay of from about 10 minutes up to about 12 hours.

[0071] The term pulsatile release is used herein in its conventional sense to refer to a drug formulation that provides release of the drug in such a way as to produce pulsed plasma profiles of the drug after drug administration.

[0072] The term immediate release is used in its conventional sense to refer to a drug formulation that provides for release of the drug immediately after drug administration. As used herein, short-term refers to any period of time up to and including about 8 hours, about 7 hours, about 6 hours, about 5 hours, about 4 hours, about 3 hours, about 2 hours, about 1 hour, about 40 minutes, about 20 minutes, or about 10 minutes after drug administration.

[0073] As used herein., rapid-offset refers to any period of time up to and including about 8 hours, about 7 hours, about 6 hours, about 5 hours, about 4 hours, about 3 hours, about 2 hours, about 1 hour, about 40 minutes, about 20 minutes, or about 10 minutes after drug administration.

Dosing

[0074] The therapeutically effective amount or dose of a compound used in the present invention will depend on the

age, sex and weight of the patient, the current medical condition of the patient and the nature of the lipoprotein abnormalities being treated. The skilled artisan will be able to determine appropriate dosages depending on these and other factors.

[0075] A suitable dose of a compound used in the present invention can be in the range of from about 0.001 mg to about 500 mg per day, such as from about 0.01 mg to about 100 mg, for example, from about 0.05 mg to about 50 mg, such as about 0.5 mg to about 25 mg per day. The dose can be administered in a single dosage or in multiple dosages, for example from 1 to 4 or more times per day When multiple dosages are used, the amount of each dosage can be the same or different. For example a dose of 1 mg per day can be administered as two 0.5 mg doses, with about a 12 hour interval between doses.

[0076] It is understood that the amount of compound dosed per day can be administered every day, every other day, every 2 days, every 3 days, every 4 days, every 5 days, etc. For example, with every other day administration, a 5 mg per day dose can be initiated on Monday with a first subsequent 5 mg per day dose administered on Wednesday, a second subsequent 5 mg per day dose administered on Friday, etc.

[0077] The compounds for use in the invention can be formulated in unit dosage form. The term "unit dosage form" refers to physically discrete units suitable as unitary dosage for subjects undergoing treatment, with each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, optionally in association with a suitable pharmaceutical carrier. The unit dosage form can be for a single daily dose or one of multiple daily doses {e.g., about 1 to 4 or more times per day). When multiple daily doses are used, the unit dosage form can be the same or different for each dose.

Exemplification of the Invention

[0078] The invention is further illustrated by the following examples, which should not be construed as further limiting. For the experiments described herein, MNA refers to 1-methylnicotinamide chloride.

Example 1: Anti-atherogenic effect of MNA after a short-term use

[0079] The anti-atherogenic effect of MNA was investigated in 20 dyslipidemic and cardiologic patients. The enrollment criteria was: high level of TG (~250 mg/dl) and/or high level of total cholesterol (TC) (≥200 mg/dl). The mean age of the patients was 57.5 (range 37-81 years). The enrolled patients were divided into two groups: dyslipidemic patients (4 pateints) and dyslipidemic patients after acute coronary failure (myocardial infarction) (12 patients). The patients were treated with MNA for 2 weeks. The MNA was administered orally, three times a day, one capsule (30 mg MNA) after meal. The 16 patients have finished clinical examination.

[0080] The plasma levels of TC, TG, and HDL were measured at baseline and after 2 weeks of therapy. The level of LDL was measured in those cases where it was possible (due to high TG level).

[0081] It has been found that MNA reduced the TC (248 vs. 212 mg/dl) (-14.50%) and TG (409 vs. 216 mg/dl) (-47.2%) levels between the base-line and 2 weeks measurements. The substantial increase of the HDL was observed after 2 weeks therapy in a group of dyslipidemic patients. The increase of the HDL was not observed after 2 weeks therapy in a group of dyslipidemic patients after acute coronary failure (myocardial infarction). The significant reduction of TG/HDL ratio (9.60 vs. 5.25) was observed.

[0082] Results of this study are shown in Tables I and II. Patient nos. 1-4 were dyslipidemic. Patient nos. 5-16 were dyslipidemic patients after acute coronary failure (myocardial infarction).

Table I

Patient no.	Sex	Age	TG			Total Cholesterol			LDL			HDL		
			visit 1 [mg/dl]	visit 2 [mg/dl]	%	visit 1 [mg/dl]	visit 2 [mg/dl]	%	visit 1 [mg/dl]	visit 2 [mg/dl]	%	visit 1 [mg/dl]	visit 2 [mg/dl]	%
1.	F	53	206	200	-2.91%	301	280	-6.98%	-	-	-	51	67	31.37%
2.	F	64	381	213	-44.09%	183	188	2.73%	-	-	-	33	45	36.36%
3.	F	81	590	160	-72.88%	293	243	-17.06%	-	-	-	42	72	71.43%
4.	M	48	269	222	-17.47%	243	231	-4.94%	-	-	-	49	42	-14.29%
5.	M	66	323	243	-24.77%	237	251	5.91%	137	162	18.25%	36	40	11.11%
6.	M	531	488	239	-51.02%	274	260	-5.11%	138	171	23.91%	38	41	7.89%
7.	M	37	387	175	-54.78%	192	208	8.33%	55	114	107.27%	60	59	-1.67%
8.	F	54	409	209	-48.90%	253	155	-38.74%	138	82	-40.58%	34	31	-8.82%
9.	M	53	478	208	-56.49%	232	130	-43.97%	-	-	-	55	41	-25.45%
10.	F	76	350	181	-48.29%	245	203	-17.14%	120	121	0.83%	55	45	-18.18%
11.	F	78	301	185	-38.54%	257	194	-24.51%	146	111	-23.97%	50	46	-8.00%
12.	M	42	305	207	-32.13%	231	159	-31.17%	126	81	-35.71%	44	37	-15.91%
13.	F	56	461	339	-26.46%	264	253	-4.17%	130	149	14.62%	42	36	-14.29%
14.	M	50	547	240	-56.12%	310	271	-12.58%	100	178	78.00%	41	45	9.76%
15.	M	48	305	259	-15.08%	221	229	3.62%	131	148	12.98%	29	29	0.00%
16.	M	61	752	181	-75.93%	242	146	-39.67%	-	-	-	49	38	-22.45%
Mean Value		67.60	409.50	216.31	-47.18%	248.63	212.56	-14.50%	122.10	131.70	7.86%	44.25	44.63	0.85%
Standard deviation		12.69	138.90	42.84		35.15	47.15		26.77	35.07		8.93	11.89	

Table II

Patient no.	Sex	Age	TG			TG/HDL			Uric Acid			Glucose		
			visit 1 [mg/dl]	visit 2 [mg/dl]	%	visit 1 [mg/dl]	visit 2 [mg/dl]	%	visit 1 [mg/dl]	visit 2 [mg/dl]	%	visit 1 [mg/dl]	visit 2 mg/dl]	%
1.	F	53	206	200	-2.91%	4.04	2.99	-26.10%	5.26	5.31	0.95%	82	89	8.54%
2.	F	64	381	213	-44.09%	11.55	4.73	-59.00%	5.4	5.26	-2.59%	143	128	-10.49%
3.	F	81	590	160	-72.88%	14.05	2.22	-84.18%	5.9	5.8	-1.69%	98	97	-1.02%
4.	M	48	269	222	-17.47%	5.49	5.29	-3.72%	6.01	7.33	21.96%	106	111	4.72%
5.	M	66	323	243	-24.77%	8.97	6.08	-32.29%	-	-	-	-	-	-
6.	M	53	488	239	-51.02%	12.84	5.83	-54.61%	8.6	-	-	167	152	-8.98%
7.	M	37	387	175	-54.78%	6.45	2.97	-54.01%		7.2	-16.28%	79	81	2.53%
8.	F	54	409	209	-48.90%	12.03	6.74	-43.95%	4.3	4.4	2.33%	83	89	7.23%
9.	M	53	478	208	-56.49%	8.69	5.07	-41.63%	14.5	8.9	-38.62%	121	90	-25.62%
10.	F	76	350	181	-48.29%	6.36	4.02	-36.79%	-	-	-	96	101	5.21%
11.	F	78	301	185	-38.54%	6.02	4.02	-33.19%	7	9.6	37.14%	110	129	17.27%
12.	M	42	305	207	-32.13%	6.93	5.59	-19.29%	6.2	6.6	6.45%	119	96	-19.33%
13.	F	56	461	339	-26.46%	10.98	9.42	-14.21%	-	-	-	82	82	0.00%
14.	M	50	547	240	-56.12%	13.34	5.33	-60.02%	-	-	-	88	96	9.09%

(continued)

Patient no.	Sex	Age	TG			TG/HDL			Uric Acid			Glucose		
			visit 1 [mg/dl]	visit 2 [mg/dl]	%	visit 1 [mg/dl]	visit 2 [mg/dl]	%	visit 1 [mg/dl]	visit 2 [mg/dl]	%	visit 1 [mg/dl]	visit 2 mg/dl]	%
15.	M	48	305	259	-15.08%	10.52	8.93	-15.08%	5.7	5.7	0.00%	95	113	18.95%
16.	M	61	752	181	-75.93%	15.35	4.76	-68.96%	6.9	5.3	-23.19%	85	-	-
Mean Value		57.50	409.50	216.31	-47.18%	9.60	5.25	-45.32%						
Standard deviation		12.69	138.90	42.84		3.46	1:96							

Example 2: Anti-atherogenic effect of MNA after a long term use

[0083] The anti-atherogenic effect of MNA was investigated in 2 dyslipidemic patients. The enrollment criteria was: high level of TG (≥250 mg/dl) and/or high level of TC (≥200 mg/dl). The patients were treated with MNA for 13 months. The MNA was administered orally, two times a day (50 mg MNA) after meal.

[0084] The plasma levels of TC, TG, and HDL were measured at baseline and during the therapy. The level of LDL was measured in those cases where it was possible (due to high TG level).

[0085] It has been found that MNA reduced significantly the TC and TG levels in these patients. An increase of HDL levels was observed after only a few months of therapy. Also, the reduction of TG/HDL ratio was observed. Results of this study are shown in Tables III-VI.

Table III

Patient 1, male, 58 years				
Time [months]	TG		Total Cholesterol	
	[mg/dl]	%	[mg/dl]	%
0	964		298	
1.5	218	-77.39%	153	-48.66%
6	255	-73.55%	177	-40.60%
12	315	-67.32%	229	-23.15%

Table IV

Patient 1, male, 58 years						
Time [months]	LDL		HDL		TG/HDL	
	[mg/dl]	%	[mg/dl]	%	[mg/dl]	%
0	nm		30.7		31.40	
1.5	81.4		28.0	-8.79%	7.79	-75.21%
6	87.0		38.6	25.73%	6.61	-78.96%
12	118.0		48.1	56.68%	6.55	-79.14%

Table V

Patient 2, male, 57 years				
Time [months]	TG		Total Cholesterol	
	[mg/dl]	%	[mg/dl]	%
0	302		365	
7	269	-10.93%	261	-28.49%
13	160	-47.02%	210	-42.47%

Table VI

Patient 2, male, 57 years						
Time [months]	LDL		HDL		TG/HDL	
	[mg/dl]	%	[mg/dl]	%	[mg/dl]	%
0	273.0		44.0		6.86	

(continued)

Patient 2, male, 57 years						
Time [months]	LDL		HDL		TG/HDL	
	[mg/dl]	%	[mg/dl]	%	[mg/dl]	%
7	128.0	-53.11%	79.0	79.55%	3.41	-50.39%
13	106.8	-60.88%	70.8	60.91%	2.26	-67.07%

Example 3: Anti-atherogenic effect of MNA after a single administration

[0086] The anti-atherogenic effect of MNA after single administration was also investigated in dyslipidemic patients. The patient was treated with 100 mg MNA. The plasma levels of TC, TG, and HDL were measured at baseline and after 1 and 3 hours. The level of LDL was not measured due to high TG level. It has been found that MNA reduced the TG (596 vs. 479 mg/dl) level between the base-line and after the administration measurements. The increase of the HDL (24.8 vs. 29.0 mg/dl) was observed after the administration. The significant reduction of TG/HDL ratio (24.0 vs. 16.5) was observed.

[0087] Results are shown in Table VII.

Table VII

male, 45 years								
Time [h]	TG		Total Cholesterol		HDL		TG/HDL	
	[mg/dl]	%	[mg/dl]	%	[mg/dl]	%	[mg/dl]	%
0	596		186		24.8		24.03	
1	566	-5.03%.	188	1.08%	25.5	2.82%	22.20	-7.64%
3	479	-19.63%	195	4.84%	29.0	16.94%	16.52	-31.27%

Example 4: MNA efficacy in the rat model of hypertriglyceridemia

[0088] Rats fed a high-fructose diet develop hypertriglyceridemia, insulin resistance and a mild degree of hypertension abnormalities that mimic metabolic syndrome in humans (Boehm and Claudi-Boehm, Scand J Clin Lab Invest Suppl. 2005; 240:3-13). To demonstrate the effect of 1-methylnicotinamide in an animal model of hypertriglyceridemia, Wistar rats were randomly divided into three groups (see Bartus et al., Pharmacol Rep. 2005; 57 Suppl:127-37.). One group was fed a control diet (basal AIN93) for 8 weeks, the second was fed an AIN93 diet supplemented with 60% fructose for 8 weeks, and the third was fed an AIN93 diet supplemented with 60% fructose that was additionally treated with 100 mg/kg of MNA for the last 4 weeks (after hypertriglicerydemia fully develops) and was given to drinking water. At the end of experiments rats were anasthetized, and blood was withdrawn and anticoagulated. Triglyceride level in plasma was measured by standard spectophotometric technique using commercially available kits. The experiment was then repeated with 10 mg/kg of MNA, which gave similar results.

[0089] The results of this experiment, as shown in Figure 1, demonstrate that 1-methylnicotinamide lowers triglyceride levels in rats fed a hypertriglyceridemic diet.

Example 5: MNA efficacy in the mice model of atheroprotection

[0090] Gene targeted animal models of atherosclerosis, such as apoE and LDL receptor double knockout mice (Ishibashi et al., Proc Natl Acad Sci USA 1994; 91: 4431-443 5; Bonthu et al., Arterioscler Thromb Vasc Biol 1997; 17: 2333-2340) represent a unique model of atherogenesis.

Methods

Animals

[0091] Female apoE/LDLR$^{-/-}$ mice on C57BL/6J background were used for experiments. The experiments were conducted according to the Guidelines for Animal Care and Treatment of the European Communities and were approved

by the Local Animal Ethics Committee. apoE/LDLR$^{-/-}$ mice were fed with standard chow. MNA was given for 2 months (100 mg/kg, 4-6 months old apoE/LDLR$^{-/-}$ mice) and effects of MNA compared to placebo-treated mice. In each group of mice (control and MNA) n=5.

Quantitation of atherosclerosis

[0092] Development of atherosclerosis was determined by cross-section (aortic roots), en-face (whole aorta) analysis and quantified semiautomatically, as described before (Jawien et al. Eur J Clin Invest; 2006; 36:141-6). Briefly, the heart and whole aorta were washed by phosphate buffered saline, then the heart and the whole aorta were removed. The heart and ascending aorta were embedded in OCT compound and snap-frozen. Ten micrometer-thick cryosections were cut and after fixation in 4% paraformaldehyde were stained with Meyer's hematoxylin and oil red-O and lesion area was measured semiautomatically in each slide using LSM Image Browser software.

[0093] The results of this experiment, as shown in Figure 2, demonstrate that 1-methylnicotinamide slows atherosclerosis progression in apoE/LDLR^{-1-} mice.

Example 6 : Safety of co-administration of MNA with statins

[0094] A group of 10 patients (4 females and 6 males, ages 38-79) on permanent therapy with simvastatin (10-20 mg/day) were selected for the study. In addition to simvastatin each patient received MNA in daily dose of 90 mg/day for six weeks. The clinical chemistry parameters were monitored during three doctor's visits: two weeks before, just before and after six weeks of MNA administration. Based on patient examination no negative effects were observed as a result of MNA co-administration along with simvastatin. Also clinical chemistry parameters, in particular liver enzymes AST and ALT, creatinine, urea, glucose and homocysteine were not changed within the measurements accuracy.

[0095] This study demonstrates that MNA co-administration with statins does not result in any adverse synergistic effects.

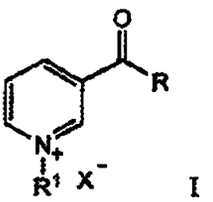
Example 7: Long term MNA use in correction of the lipoprotein profile in patients on permanent therapy with statins

[0096] A group of 8 patients (5 females and 3 males, ages 59-85) on permanent therapy with simvastatin or atorvastatin (10 - 20 mg/day) were selected for the study. MNA in a daily dose of 90 -180 mg was co-administrated for a period of 3 to 42 months. The liporotein levels for each patient were monitored in every 1 to 3 months. In general, a long term co-administration of MNA resulted in the reduction of triglyceride (TG) level. The changes varied from patient to patient within a limit -5% to -42%. The appropriate changes in LDL were within -12% to +17% and in HDL within -6% to +37%. A particularly remarkable increase in HDL was observed in patients with a low starting HDL level (<40 mg/dl).

[0097] This example demonstrates that a long term co-administration of MNA with statins results in a decrease of TG and increase of HDL. Neither patients nor doctors involved with this study have declared any negative side effects from statin use, which could be associated with MNA co-administration.

Claims

1. A pharmaceutical composition comprising a statin and a 1-methylnicotinamide salt of Formula I:



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wherein R represents NH_2; R^1 represents methyl; and X^- is a physiologically suitable counter-anion.

2. The pharmaceutical composition of claim 1 wherein the salt is chloride, benzoate, salicylate, acetate, citrate or lactate.

3. The pharmaceutical composition of claim 1 wherein the salt of Formula I is 1-methylnicotinamide chloride.

4. The pharmaceutical composition of claims 1 to 2, wherein the statin is mevastatin, lovastatin, simvastatin, pravastatin, fluvastatin, pitavastatin, atorvastatin, cerivastatin, rosuvastatin, or pentostatin, or a pharmaceutically acceptable salt, solvate, clathrate, polymorph, prodrug, or pharmacologically active metabolite thereof.

5. The pharmaceutical composition of any one of claims 1 to 4, together with one or more pharmaceutically acceptable carriers, diluents or excipients.

6. The pharmaceutical composition of any one of claims 1 to 5, wherein the pharmaceutical composition is in tablet form.

7. The pharmaceutical composition of any one of claims 1 to 5, wherein the pharmaceutical composition is in capsule form.

8. The pharmaceutical composition of any one of claims 1 to 5, wherein the pharmaceutical composition is in controlled release or sustained release form.

9. A combination comprising a statin and a 1-methylnicotinamide salt of Formula I as defined in any one of claims 1 to 4 for use in therapy.

10. The combination of claim 9 for use in the treatment of dyslipidemia or atherosclerosis.

11. Use of a combination comprising a statin and a 1-methylnicotinamide salt of Formula I as defined in any one of claims 1 to 4 for preparing a pharmaceutical composition for treating dyslipidemia or atherosclerosis.

12. The combination or use of claims 10 to 11, wherein the statin and the salt of Formula I are co-administered to the subject.

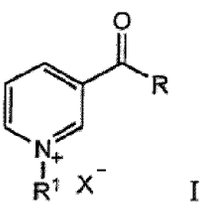
13. The combination or use of claims 10 to 11, wherein the statin and the salt of Formula I are administered sequentially to the subject.

14. The combination or use of any one of claims 10 to 13, wherein dyslipidemia is a low HDL level, a high LDL level, high triglycerides level or high total cholesterol, or any combination thereof

15. The combination or use of any one of claims 10 to 14, wherein dyslipidemia is associated with atherosclerosis.

Patentansprüche

1. Pharmazeutische Zusammensetzung, umfassend ein Statin und ein 1-Methylnicotinamid-Salz der Formel I:



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worin R NH_2 darstellt; R^1 Methyl darstellt; und X^- ein physiologisch annehmbares Gegenion ist.

2. Pharmazeutische Zusammensetzung nach Anspruch 1, worin das Salz Chlorid, Benzoat, Salicylat, Acetat, Citrat oder Laktat ist.

3. Pharmazeutische Zusammensetzung nach Anspruch 1, worin das Salz der Formel I 1-Methylnicotinamidchlorid ist.

4. Pharmazeutische Zusammensetzung nach Anspruche 1 bis 2, worin das Statin Mevastatin, Lovastatin, Simvastatin, Pravastatin, Fluvastatin, Pitavastatin, Atorvastatin, Cerivastatin, Rosuvastatin, oder Pentostatin, oder ein pharmazeutisch annehmbares Salz, Solvat, Clathrat, Polymorf, Prodrug, oder pharmakologisch aktiv Metabolit davon, ist.

5. Pharmazeutische Zusammensetzung nach einem der Ansprüche 1 bis 4, zusammen mit einem oder mehreren pharmazeutisch annehmbaren Träger, Verdünnungsmittels oder Hilfsstoffe.

6. Pharmazeutische Zusammensetzung nach einem der Ansprüche 1 bis 5, worin die pharmazeutische Zusammensetzung in Tablettenform ist.

7. Pharmazeutische Zusammensetzung nach einem der Ansprüche 1 bis 5, worin die pharmazeutische Zusammensetzung in Kapselform ist.

8. Pharmazeutische Zusammensetzung nach einem der Ansprüche 1 bis 5, worin die pharmazeutische Zusammensetzung in einer Form mit kontrollierter- oder verzögerter Freisetzung ist.

9. Kombination enthaltend ein Statin und ein 1-Methylnicotinamid-Salz der Formel I wie in einem der Ansprüche 1 bis 4 definiert, zur Anwendung in der Therapie.

10. Kombination nach Anspruch 9 zur Anwendung in der Therapie von Dyslipidämie oder Arteriosklerose.

11. Anwendung von der Kombination umfassend ein Statin und ein 1-Methylnicotinamid-Salz der Formel I wie in einem der Ansprüche 1 bis 4 definiert, zur Vorbereitung einer pharmazeutischen Zusammensetzung zur Behandlung von Dyslipidämie oder Arteriosklerose.

12. Kombination oder Anwendung nach einem der Ansprüche 10 bis 11, worin das Statin und das Salz der Formel I gleichzeitig dem Subjekt verabreicht werden.

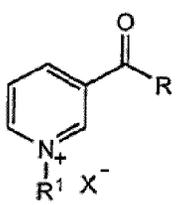
13. Kombination oder Anwendung nach einem der Ansprüche 10 bis 11, worin das Statin und das Salz der Formel sequenziell dem Subjekt verabreicht werden.

14. Kombination oder Anwendung nach einem der Ansprüche 10 bis 13, worin Dyslipidämie eine niedrige HDL, eine hohe LDL-Spiegel, eine hohe Triglyzeridespiegel oder hohe Gesamtcholesterol, oder irgendeine Kombination davon ist.

15. Kombination oder Anwendung nach einem der Ansprüche 10 bis 14, worin Dyslipidämie mit Atherosklerose assoziiert sind.

Revendications

1. Une composition pharmaceutique comprenant une statine et un sel de 1-méthylnicotinamide de la formule I:



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dans laquelle R représente NH_2; R^1 représente méthyl; et X^- est un contre-ion physiologiquement acceptable.

2. La composition pharmaceutique selon la revendication 1, dans laquelle le sel est le chlorure, le benzoate, le salicylate, l'acétate, le citrate ou le lactate.

3. La composition pharmaceutique selon la revendication 1, dans laquelle le sel de la formule I est le chlorure de 1-méthylnicotinamide.

4. La composition pharmaceutique selon les revendications 1 à 2, dans laquelle la statine est mevastatine, lovastatine, simvastatine, pravastatine, fluvastatine, pitavastatine, atorvastatine, cerivastatine, rosuvastatine, ou pentostatine, ou un de leurs sels pharmaceutiquement acceptables, solvates, clathrates, polymorphs, promédicaments, ou phar-

macologiquement actives métabolites.

5. La composition pharmaceutique selon l'une quelconque des revendications 1 à 4, avec un ou plusieurs des véhicules, diluants ou excipients pharmaceutiquement acceptables.

6. La composition pharmaceutique selon l'une quelconque des revendications 1 à 5, dans laquelle la composition est sous forme de comprimé.

7. La composition pharmaceutique selon l'une quelconque des revendications 1 à 5, dans laquelle la composition est sous forme de capsule.

8. La composition pharmaceutique selon l'une quelconque des revendications 1 à 5, dans laquelle la composition est sous forme à libération contrôlée ou à libération prolongée.

9. Une combinaison comprenant une statine et un sel de 1-méthylnicotinamide de la formule 1 telles que définies dans revendications 1 à 4 destiné à être utilisé en thérapie.

10. La combinaison selon la revendication 9 destiné à être utilisé dans le traitement de la dyslipidémie ou de l'athérosclérose.

11. Utilisation de la combinaison comprenant une statine et un sel de 1-méthylnicotinamide de la formule 1 telles que définies dans revendications 1 à 4 pour la préparation de la médicament pour traitement de la dyslipidémie ou de l'athérosclérose.

12. La combination ou l'utilisation selon la revendication 10 ou 11, dans laquelle la statine et le sel de la formule I sont administrées au sujet en association.

13. La combination ou l'utilisation selon la revendication 10 ou 11, dans laquelle la statine et le sel de la formule I sont administrées au sujet en séquence.

14. La combination ou l'utilisation selon la revendication 10 ou 11, dans laquelle la dyslipidémie est un faible taux de cholestérol HDL, un taux élevé de cholestérol LDL, un taux élevé des triglycérides ou un taux élevé de le cholestérol total, ou une combinaison des ceux-ci.

15. La combination ou l'utilisation selon l'une quelconque des revendications 10 à 14, dans laquelle la dyslipidémie est associée à l'athérosclérose.

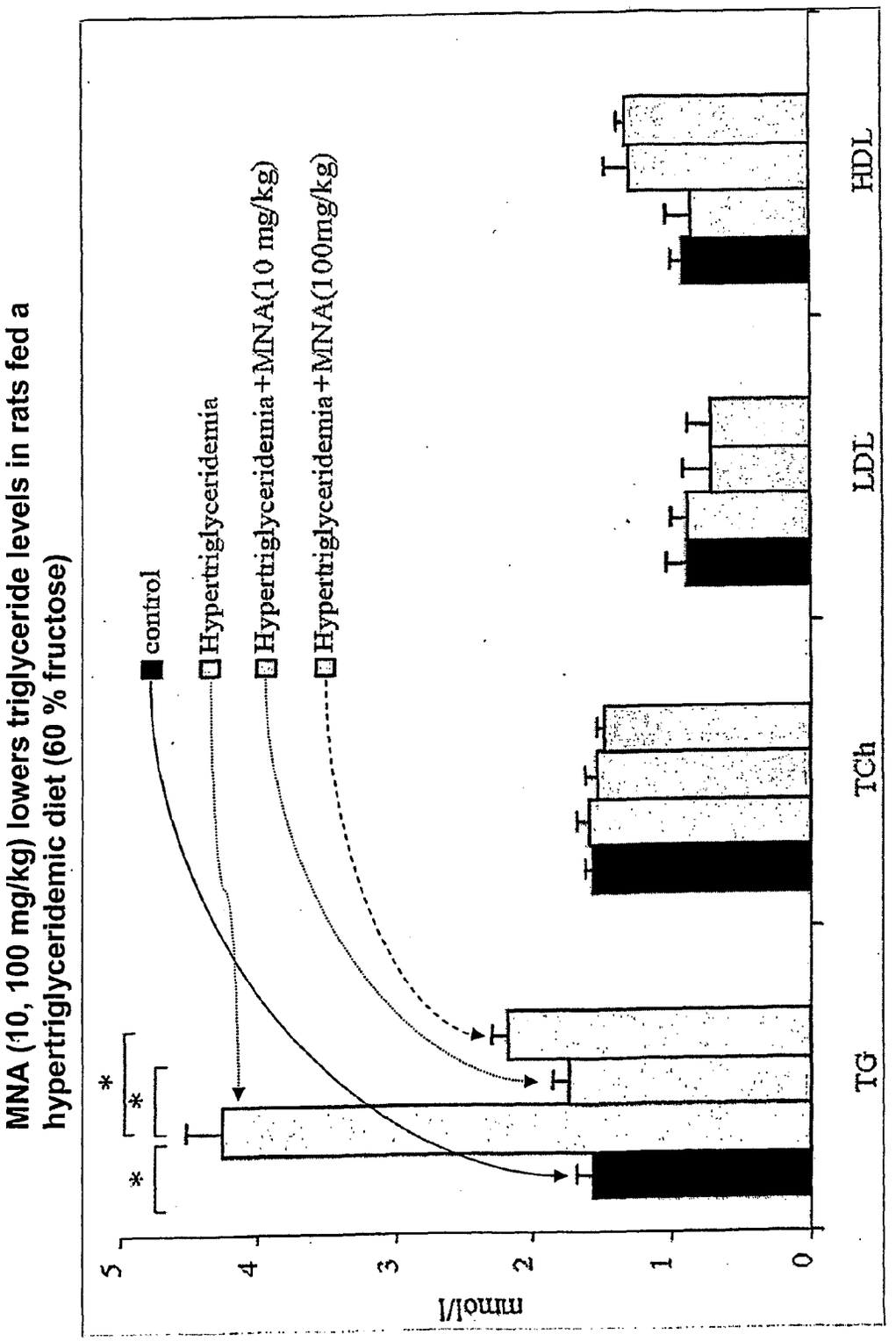
MNA (10, 100 mg/kg) lowers triglyceride levels in rats fed a hypertriglyceridemic diet (60 % fructose)
control
Hypertriglyceridemia
Hypertriglyceridemia+MNA(10 mg/kg)
Hypertriglyceridemia+MNA(100mg/kg)
mmol/l
0
1
2
3
4
5
*
*
*
TG
TCh
LDL
HDL

Fig. 1

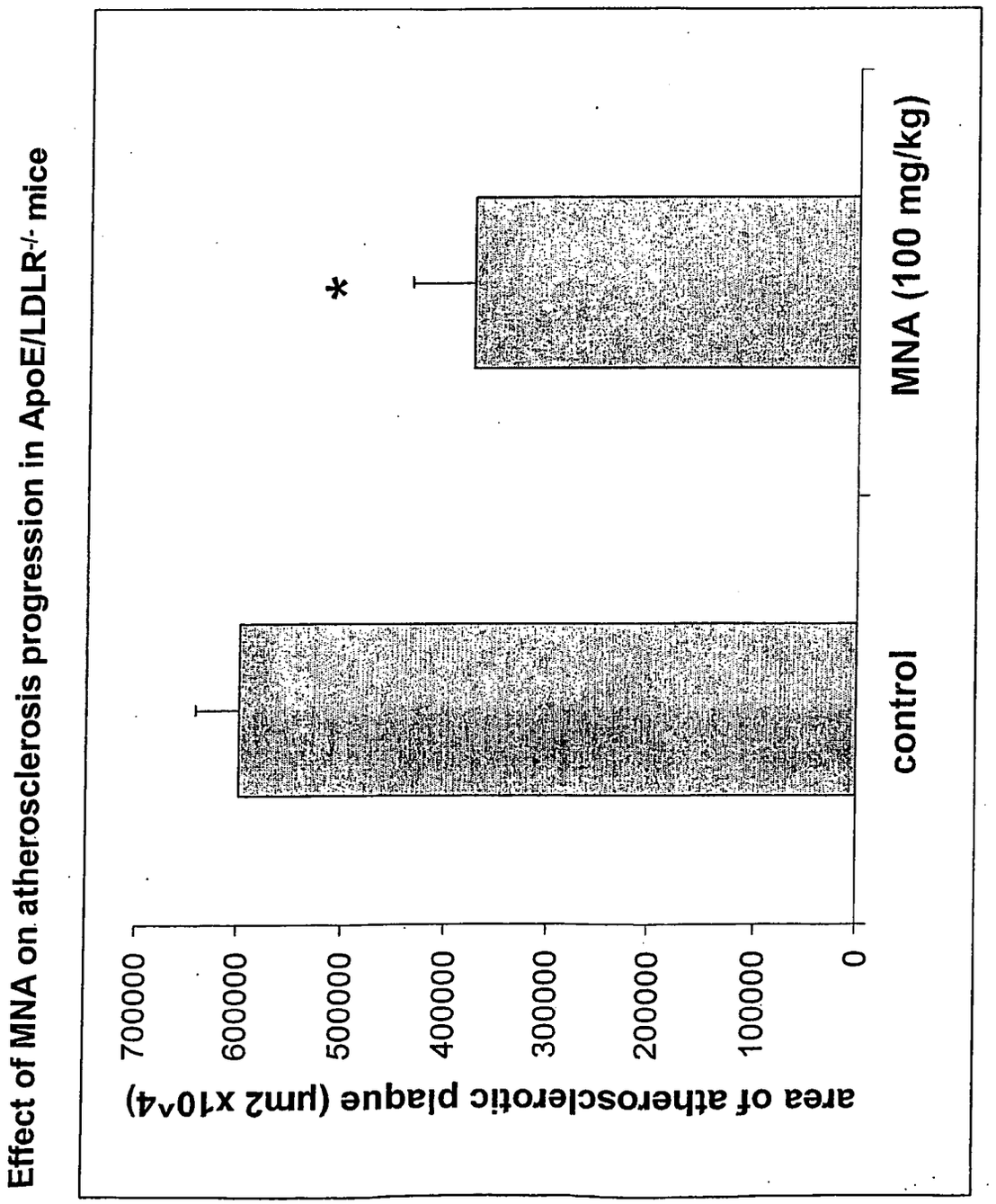
Effect of MNA on atherosclerosis progression in ApoE/LDLR-/- mice
area of atherosclerotic plaque (µm2 x10^4)
700000
600000
500000
400000
300000
200000
100000
0
*
control
MNA (100 mg/kg)

Fig. 2

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