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Rader

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(54) **METHODS FOR TREATING DISORDERS OR DISEASES ASSOCIATED WITH HYPERLIPIDEMIA AND HYPERCHOLESTEROLEMIA WHILE MINIMIZING SIDE EFFECTS**

(76) Inventor: **Daniel J. Rader**, Philadelphia, PA (US)

Correspondence Address:
GOODWIN PROCTER LLP
PATENT ADMINISTRATOR
53 STATE STREET, EXCHANGE PLACE
BOSTON, MA 02109-2881 (US)

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(57) **ABSTRACT**

The present invention provides methods and compositions for treating hyperlipidemia and/or hypercholesterolemia comprising administering to the subject an effective amount of an MTP inhibitor to inhibit hyperlipidemia and/or hypercholesterolemia in said subject, wherein said administration comprises an escalating series of doses of the MTP inhibitor. In some embodiments the method comprises administering at least three step-wise, increasing dosages of the MTP inhibitor to the subject. In some embodiments, the method further comprises the administration of one or more other lipid modifying compounds.

METHODS FOR TREATING DISORDERS OR DISEASES ASSOCIATED WITH HYPERLIPIDEMIA AND HYPERCHOLESTEROLEMIA WHILE MINIMIZING SIDE EFFECTS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a national phase application under 35 U.S.C. § 371 of PCT/US05/007435 filed Mar. 7, 2005 which in turn claims priority benefit of U.S. Ser. No. 60/550,915, filed Mar. 5, 2004, all of which are hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

[0002] The present invention generally relates to therapy for hypercholesterolemia and hyperlipidemia.

BACKGROUND OF THE INVENTION

[0003] Hypercholesterolemia is a well-known risk factor for ASCVD, the major cause of mortality in the Western world. Numerous epidemiological studies have clearly demonstrated that pharmacological lowering of total cholesterol (TC) and Low-density Lipoprotein (LDL) Cholesterol (LDL-C) is associated with a significant reduction in clinical cardiovascular events. Hypercholesterolemia is often caused by a polygenic disorder in the majority of cases and modifications in lifestyle and conventional drug treatment are usually successful in reducing cholesterol levels. However, in few cases, as in familial hypercholesterolemia (FH), the cause is a monogenic defect and the available treatment in homozygous patients can be much more challenging and far from optimal because LDL-C levels remain extremely elevated despite aggressive use of combination therapy. Therefore, for this group of high-risk patients, effective medical therapy is urgently needed.

[0004] Triglycerides are common types of fats (lipids) that are essential for good health when present in normal amounts. They account for about 95 percent of the body's fatty tissue. Abnormally high triglyceride levels may be an indication of such conditions as cirrhosis of the liver, underactive thyroid (hypothyroidism), poorly controlled diabetes, or pancreatitis (inflammation of the pancreas). Researchers have identified triglycerides as an independent risk factor for heart disease.

[0005] Higher-than-normal triglyceride levels are often associated with known risk factors for heart disease, such as low levels of HDL ("good") cholesterol, high levels of LDL ("bad") cholesterol and obesity. Triglycerides may also contribute to thickening of artery walls—a physical change believed to be a predictor of atherosclerosis.

[0006] Therefore, high triglyceride levels are at least a warning sign that a patient's heart health may be at risk. In response, physicians may be more likely to stress the importance of losing weight, getting enough exercise, quitting smoking, controlling diabetes and other strategies that patients can use to protect their own cardiovascular health.

[0007] A large number of genetic and acquired diseases can result in hyperlipidemia. They can be classified into primary and secondary hyperlipidemic states. The most common causes of the secondary hyperlipidemias are diabetes mellitus, alcohol abuse, drugs, hypothyroidism, chronic renal failhypercholesterolemia, familial combined hyperlipidemia, familial hypercholesterolemia, remnant hyperlipidemia, chylomicronemia syndrome and familial hypertriglyceridemia.

[0008] A number of treatments are currently available for lowering serum cholesterol and triglycerides. However, each has its own drawbacks and limitations in terms of efficacy, side-effects and qualifying patient population.

[0009] Bile-acid-binding resins are a class of drugs that interrupt the recycling of bile acids from the intestine to the liver; e.g., cholestyramine (Questran Light®, Bristol-Myers Squibb), and colestipol hydrochloride (Colestid®, The Upjohn Company). When taken orally, these positively-charged resins bind to the negatively charged bile acids in the intestine. Because the resins cannot be absorbed from the intestine, they are excreted carrying the bile acids with them. The use of such resins, however, at best only lowers serum cholesterol levels by about 20%, and is associated with gastrointestinal side-effects, including constipation and certain vitamin deficiencies. Moreover, since the resins bind other drugs, other oral medications must be taken at least one hour before or four to six hours subsequent to ingestion of the resin; thus, complicating heart patient's drug regimens.

[0010] The statins are cholesterol-lowering agents that block cholesterol synthesis by inhibiting HMGCoA reductase—the key enzyme involved in the cholesterol biosynthetic pathway. The statins, e.g., lovastatin (Mevacor®, Merck & Co., Inc.), simvastatin (Zocor®, Merck & Co., Inc.), atorvastatin (Lipitor®, Pfizer), rosuva (Crestor®, Astra Zeneca) and pravastatin (Pravachol®, Bristol-Myers Squibb Co.), and combinations thereof, are sometimes used in combination with bile-acid-binding resins. Statins significantly reduce serum cholesterol and LDL-serum levels, and slow progression of coronary atherosclerosis. However, serum HDL cholesterol levels are only moderately increased. The mechanism of the LDL lowering effect may involve both reduction of VLDL concentration and induction of cellular expression of LDL-receptor, leading to reduced production and/or increased catabolism of LDLs. Side effects, including liver and kidney dysfunction are associated with the use of these drugs (Physicians Desk Reference, Medical Economics Co., Inc., Montvale, N.J., 2004; hereinafter "PDR"). The FDA has approved atorvastatin to treat rare but urgent cases of familial hypercholesterolemia.

[0011] Ezetimibe is a cholesterol absorption inhibitor which reduces the amount of cholesterol absorbed by the body. Ezetimibe is used to reduce the amount of total cholesterol, LDL cholesterol (by about 18%), and apolipoprotein B. Ezetimibe is often used with a low cholesterol diet and, in some cases, other cholesterol lowering medications.

[0012] Niacin, or nicotinic acid, is a water soluble vitamin B-complex used as a dietary supplement and antihyperlipidemic agent. Niacin diminishes production of VLDL and is effective at lowering LDL. In some cases, it is used in combination with bile-acid binding resins. NIASPAN® has been approved to prevent recurrent heart attacks in patients with high cholesterol. Niacin can increase HDL when used at adequate doses, however, its usefulness is limited by serious side effects when used at such high doses.

[0013] Fibric acid derivatives ("fibrates") are a class of lipid-lowering drugs used to treat various forms of hyperlipidemia (i.e., elevated serum triglycerides) which may also be associated with hypercholesterolemia. Fibrates appear to

able. Fibrates are mainly used to lower high triglyceride levels. Although fibrates typically do not appear as effective as statins in lowering total cholesterol and LDL cholesterol levels, they are sometimes used in combination with statins or other medications to lower very high cholesterol levels. For example, fibrates are also sometimes added to statins to raise HDL cholesterol levels. In the United States, fibrates have been approved for use as antilipidemic drugs, but have not received approval as hypercholesterolemia agents. For example, clofibrate (Atromid-S®, Wyeth-Ayerst Laboratories) is an antilipidemic agent which acts to lower serum triglycerides by reducing the VLDL fraction. Although serum cholesterol may be reduced in certain patient subpopulations, the biochemical response to the drug is variable, and is not always possible to predict which patients will obtain favorable results. Atromid-S® has not been shown to be effective for prevention of coronary heart disease. The chemically and pharmacologically related drug, gemfibrozil (Lopid®, Parke-Davis) is a lipid regulating agent which moderately decreases serum triglycerides and VLDL cholesterol, and moderately increases HDL cholesterol—the HDL_2 and HDL_3 subfractions as well as both ApoA-I and A-II (i.e., the AI/AII-HDL fraction). However, the lipid response is heterogeneous, especially among different patient populations. Moreover, while prevention of coronary heart disease was observed in male patients between 40-55 without history or symptoms of existing coronary heart disease, it is not clear to what extent these findings can be extrapolated to other patient populations (e.g., women, older and younger males). Indeed, no efficacy was observed in patients with established coronary heart disease. Fenofibrate (Tricor, Secalip) is also used to reduce levels of cholesterol and triglycerides. Serious side-effects have been associated with the use of several fibrates including toxicity such as malignancy, (especially gastrointestinal cancer), gallbladder disease and an increased incidence in non-coronary mortality. Fibrates are often not indicated for the treatment of patients with high LDL or low HDL as their only lipid abnormality (Physician's Desk Reference, 2004, Medical Economics Co., Inc. Montvale, N.J.).

[0014] Oral estrogen replacement therapy may be considered for moderate hypercholesterolemia in post-menopausal women. However, increases in HDL may be accompanied with an increase in triglycerides. Estrogen treatment is, of course, limited to a specific patient population (postmenopausal women) and is associated with serious side effects including induction of malignant neoplasms, gall bladder disease, thromboembolic disease, hepatic adenoma, elevated blood pressure, glucose intolerance, and hypercalcemia.

[0015] Homozygous familial hypercholesterolemia (hoFH) is a serious life-threatening genetic disease caused by homozygosity or compound heterozygosity for mutations in the low density lipoprotein (LDL) receptor. Total plasma cholesterol levels are generally over 500 mg/dl and markedly premature atherosclerotic vascular disease is the major consequence. Untreated, most patients develop atherosclerosis before age 20 and generally do not survive past age 30. The primary goal of therapy consists of controlling the hypercholesterolemia to delay the development of atherosclerotic cardiovascular disease (ASCVD). However, patients diagnosed with hoFH are largely unresponsive to conventional drug therapy and have limited treatment options. A mean LDL-C reduction of only about 5.5% has been recently reported in mg/day). The addition of ezetimibe 10 mg/day to this regimen resulted in a total reduction of LDL-C levels of 27%, which is still far from optimal. Several non-pharmacological options have also been tested. Surgical interventions, such as portacaval shunt and ileal bypass have resulted only in partial and transient LDL-C lowering. Orthotopic liver transplantation has been demonstrated to substantially reduce LDL-C levels in hoFH patients, but obvious disadvantages and risks are associated with this approach. Although hoFH could be an excellent model for gene therapy, this modality of treatment is not foreseeable in the near future due to the limitations on the availability of safe vectors that provide long-term expression of LDL receptor gene. Thus, the current standard of care in hoFH is LDL apheresis, a physical method of filtering the plasma of LDL-C which as monotherapy can transiently reduce LDL-C by about 50%. Apheresis uses affinity columns to selectively remove apoB-containing lipoproteins. However, because of rapid re-accumulation of LDL-C in plasma, apheresis has to be repeated frequently (every 1-2 weeks) and requires 2 separate sites for IV access. Although anecdotally this procedure may delay the onset of atherosclerosis, it is laborious, expensive, and not readily available. Furthermore, although it is a procedure that is generally well tolerated, the fact that it needs frequent repetition and IV access can be challenging for many of these young patients. Therefore, there is a tremendous unmet medical need for new medical therapies for hoFH.

[0016] Patients with heterozygous FH can usually be successfully treated with combination drug therapy to lower the LDL-C to acceptable levels. In contrast, hoFH is unresponsive to conventional drug therapy and thus there are limited treatment options. Specifically, treatment with statins, which reduce LDL-C by inhibiting cholesterol synthesis and upregulating the hepatic LDL receptor, have negligible effect in patients whose LDL receptors are non-existent or defective.

[0017] In July 2004, the NCEP published a paper entitled "Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines", updating certain elements of the "Adult Treatment Panel III (ATP III)" cholesterol guidelines released in 2001. For high-risk patients, individuals who have coronary heart disease (CHD) or disease of the blood vessels to the brain or extremities, or diabetes, or multiple (2 or more) risk factors that give them a greater than 20 percent chance of having a heart attack within 10 years, the ATP III update recommends that the overall goal for high-risk patients is still an LDL less than 100 mg/dL with a therapeutic option to set the goal at an LDL less than 70 mg/dL for very high-risk patients, those who have had a recent heart attack, or those who have cardiovascular disease combined with either diabetes, or severe or poorly controlled risk factors (such as continued smoking), or metabolic syndrome (a cluster of risk factors associated with obesity that includes high triglycerides and low HDL cholesterol). The ATP III update also recommends consideration of drug treatment in addition to lifestyle therapy for LDL levels 100 mg/dL or higher in high-risk patients, and characterizes drug treatment as optional for LDL less than 100 mg/dL. For moderately high-risk patients, individuals who have multiple (2 or more) CHD risk factors together with a 10-20 percent risk for a heart attack within 10 years, the ATP III update recommends the overall goal for moderately high-risk

mg/dL, and to use drug treatment if LDL is 100-129 mg/dL. For high-risk and moderately high-risk patients, the ATP III update advises that the intensity of LDL-lowering drug treatment in high-risk and moderately high-risk patients be sufficient to achieve at least a 30 percent reduction in LDL levels.

[0018] Patients suffering from severe hypercholesterolemia may also be unable to reach the new goals for LDL and HDL described above. For example, a large number of patients may be unable to attain LDL levels less than 70 using maximally tolerated current methodologies.

[0019] Abetalipoproteinemia is a rare genetic disease characterized by extremely low cholesterol and TG levels, absent apolipoprotein (apo) B-containing lipoproteins in plasma, fat malabsorption, severe vitamin E deficiency, and progressive spinocerebellar and retinal degeneration. It has been determined that mutations in the MTP were the genetic cause of abetalipoproteinemia. MTP is responsible for transferring lipids, particularly TG, onto the assembling chylomicron and VLDL particles in the intestine and the liver, respectively. Although the mechanisms by which lipoproteins are formed are not completely understood, it is currently believed that the assembly of apoB containing lipoproteins requires two steps. The first step occurs within the endoplasmic reticulum that involves the synthesis of particles that contain only a small fraction of the lipid core found in the secreted lipoprotein. A larger core of lipid is added to the nascent particle in a second step. MTP is thought to be essential for the transfer of lipid to the apoB during the first step of the process. In the absence of functional MTP, chylomicrons and VLDL are not effectively assembled or secreted in the circulation and apoB is likely targeted for degradation. VLDL serves as the metabolic precursor to LDL and the inability to secrete VLDL from the liver results in the absence of LDL in the blood. The concept that MTP may regulate apoB lipoprotein assembly is supported by observations in mice models. In heterozygous knockout mice MTP mRNA, protein and activity have been reported approximately half of normal and the apoB plasma concentration was reduced about 30%. Dramatic reduction of apoB-100 concentration in plasma was also seen in liver-specific MTP knockout mice. The finding that MTP is the genetic cause of abetaliproteinemia and that is involved in apoB-containing particles assembly and secretion led to the concept that pharmacologic inhibition of MTP might be a successful strategy for reducing atherogenic lipoproteins levels in humans.

[0020] Because of the tremendous impact on the treatment of atherosclerosis and cardiovascular disease that can be derived from the pharmacologic inhibition of hepatic secretion of apoB containing lipoproteins, several MTP inhibitors have been developed. Both in vitro and in vivo animal studies with these compounds support the concept that inhibition of MTP results in inhibition of apoB containing lipoproteins secretion and consequent reduction of plasma cholesterol levels. Interestingly, the animal studies cited above had been conducted in Watanabe-heritable hyperlipidemic (WHHL) rabbits and LDLR-/-mice, two models for hoFH.

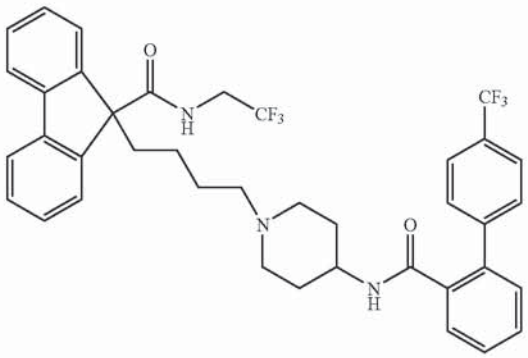
[0021] Bristol-Myers Squibb (BMS) developed a series of compounds, including BMS-201038, as potent inhibitors of MTP-mediated neutral lipid transfer activity. These compounds are described, for example, in U.S. Pat. Nos. 5,789, tors are described throughout U.S. Pat. No. 6,066,653, in particular in columns 3-28. In in vitro studies, BMS-201038 appears to inhibit lipid transfer by directly binding to MTP. In cell culture studies, the IC_{50} for inhibition of apoB secretion by BMS-201038 was much lower than that for apoAI secretion (0.8 nM vs 6.5 μM), indicating that the compound is a highly selective inhibitor of apoB secretion. The efficacy to inhibit accumulation of triglyceride-rich particles in plasma of rats after injection of Triton is similar in both fed and fasted states, suggesting that both intestinal and hepatic lipoprotein secretions are inhibited by this compound. Six-month toxicity studies were conducted by BMS in rats and dogs and their results are detailed in IND# 50,820. Doses tested were 0, 0.02, 0.2, 2.0, and 20 mg/kg in rats and 0, 0.01, 0.1, 1.0, and 10 mg/kg in dogs. Dose-related lipid accumulation in the liver and small intestine correlated with decrease in serum TG and cholesterol levels. These changes are a consequence of the pharmacologic effects of BMS-201038. In rats, but not in dogs, doses of 0.2 mg/kg and higher were associated with subacute inflammation and single-cell necrosis of hepatocytes and histiocytosis (phospholipidosis) in the lungs. The hepatic accumulation of lipids was reversed in rats at the end of a 1-month washout period. Studies in animals indicated that BMS-201038 effectively reduced plasma cholesterol levels in a dose dependent manner. BMS-201038 was found to be effective in reducing cholesterol levels in rabbits that lack a functional LDL receptor: The ED_{50} value for lowering cholesterol was 1.9 mg/kg and a dose of 10 mg/kg essentially normalized cholesterol levels with no alteration in plasma AST or ALT. This study, conducted in the best accepted animal model for the homozygous FH, indicated that MTP inhibition by BMS-201038 might be effective in substantially reducing cholesterol levels in patients with hoFH.

[0022] Clinical development of BMS-201038 as a drug for large scale use in the treatment of hypercholesterolemia has been discontinued, because of significant and serious hepatotoxicities. For example, gastrointestinal side effects, elevation of serum transaminases and hepatic fat accumulation were observed, primarily at 25 mg/day or higher doses. Thus, there is a need to develop methods for treating hyperlipidemia and/or hypercholesterolemia that are efficacious in lowering serum cholesterol and LDL, increasing HDL serum levels, preventing coronary heart disease, and/or treating diseases associated with hyperlipidemia and/or hypercholesterolemia, without the side-effects associated with known treatments.

SUMMARY OF THE INVENTION

[0023] The present invention relates to methods of treating disorders associated with hypercholesterolemia and/or hyperlipidemia.

[0024] In some embodiments the invention relates to methods of treating a subject suffering from a disorder associated with hyperlipidemia and/or hypercholesterolemia. The methods comprise administering to the subject an amount of an MTP inhibitor effective to ameliorate the disorder, wherein said administration comprises at least three step-wise,



or a pharmaceutically acceptable salt thereof or the piperidine N-oxide thereof.

[0025] The present invention further provides methods for inhibiting MTP in a subject in need thereof. The methods comprise administering to the subject an amount of an MTP inhibitor effective to inhibit MTP, wherein said administration comprises at least three step-wise, increasing dosages of the MTP inhibitor.

[0026] The present invention provides kits for treating a disorder associated with hyperlipidemia and/or hypercholesterolemia in a subject, comprising at least three sets of pharmaceutical dosage units; and instructions for use.

DETAILED DESCRIPTION OF THE INVENTION

[0027] The present invention is based on the surprising discovery that one may treat an individual who has hyperlipidemia and/or hyperlcholesterolemia with an MTP inhibitor in a manner that results in the individual not experiencing side-effects normally associated with the inhibitor, or experiencing side-effects to a lesser degree. Accordingly, the present invention provides methods of treating a subject suffering from a disorder associated with hyperlipidemia while reducing side-effects, the method comprising the step of administering to the subject an effective amount of the MTP inhibitor to ameliorate hyperlipidemia and/or hypercholesterolemia in the subject according to a treatment regimen that reduces and/or eliminates side-effects associated with the use of the inhibitors.

[0028] By "treatment" is meant at least an amelioration of the symptoms associated with the pathological condition afflicting the host as well as an amelioration of the side-effects associated with the MTP inhibitor seen in patients treated in accordance with traditional treatment regimens making use of MTP inhibitors. "Amelioration" is used in a broad sense to refer to at least a reduction in the magnitude of a parameter, e.g. symptom, associated with the pathological condition being treated, such as elevated plasma VLDL or triglyceride levels, or with a side effect of treatment using the inhibitor, such as GI side-effects or hepatobiliary side-effects. As such, treatment also includes situations where the pathological condition, or at least symptoms associated therewith, are completely inhibited, e.g. prevented from happening, or stopped, e.g. terminated, such that the host no longer suffers from the pathological condition, or at least the symptoms that charac-

[0029] The present invention also provides methods of treating diseases/disorders associated with hypercholesterolemia and/or hyperlipidemia comprising administering to a subject an MTP inhibitor and a further lipid modifying compound. The methods reduce and/or eliminate side-effects associated with the use of MTP inhibitors.

[0030] As used herein, the phrase "disorders associated with hyperlipidemia and/or hypercholesterolemia" refers to diseases and disorders related to or caused by elevated lipid or cholesterol levels. Such diseases and disorders include, without limitation, hypercholesterolemia, severe hypercholesterolemia, familial combined hyperlipidemia, familial hypercholesterolemia, remnant hyperlipidemia, chylomicronemia syndrome and familial hypertriglyceridemia. In some embodiments, the disease is severe hypercholesterolemia. In some embodiments, the disease is homozygous/heterozygous familial hypercholesterolemia. In some embodiments the disease is hypertriglyceridemia.

[0031] Microsomal triglyceride transfer protein (MTP) is known to catalyze the transport of triglyceride and cholesteryl ester by preference to phospholipids such as phosphatidylcholine. It was demonstrated by D. Sharp et al., Nature (1993) 365:65 that the defect causing abetalipoproteinemia is in the MTP gene. This indicates that MTP is required for the synthesis of Apo B-containing lipoproteins such as VLDL, the precursor to LDL. It therefore follows that an MTP inhibitor would inhibit the synthesis of VLDL and LDL, thereby lowering levels of VLDL, LDL, cholesterol and triglyceride in humans.

[0032] MTP inhibitors belong to the class of polyarylcarboxamides. MTP inhibitors, methods of use and preparation thereof are known to the art skilled and are described, inter alia, in WO 96/26205; U.S. Pat. No. 5,760,246; WO 96/40640; WO-98/27979. Canadian Patent Application Ser. No. 2,091,102, U.S. application Ser. No. 117,362, WO 92/26205 published Aug. 29, 1996, U.S. application Ser. No. 472,067, filed Jun. 6, 1995, U.S. application Ser. No. 548,811, filed Jan. 11, 1996, U.S. provisional application Ser. No. 60/017,224, filed May 9, 1996, U.S. provisional application Ser. No. 60/017,253, filed May 10, 1996, U.S. provisional application Ser. No. 60/017,254, filed May 10, 1996, U.S. provisional application Ser. No. 60/028,216, filed Oct. 1, 1996, U.S. Pat. No. 5,595,872, U.S. Pat. No. 5,789,197, U.S. Pat. No. 5,883,109, and U.S. Pat. No. 6,066,653. All of the above, including structures, are incorporated herein by reference.

[0033] Pharmacologic inhibition of MTP with Bristol-Myers Squibb's BMS-201038, a potent inhibitor of MTP, has been shown to reduce low density lipoprotein cholesterol (LDL-C) by up to 65% in healthy volunteers with hypercholesterolemia. Despite these impressive LDL-C reductions, steatorrhea, elevation of serum transaminases and hepatic fat accumulation were observed, primarily at 25 mg/day or higher doses. Thus, Bristol-Myers Squibb decided that these side effects made it unlikely that BMS-201038 could be developed as a drug for large scale use in the treatment of hypercholesterolemia. Combinations using MTP inhibitors and other cholesterol or triglyceride drugs have been previously disclosed (U.S. Pat. Nos. 6,066,653 and 5,883,109) but suffer the same drawbacks as described above for MTP inhibitors used alone.

[0034] In some embodiments the MTP inhibitors are pip-

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