Treatment of NAFLD and NASH

Technical field

[0001] This invention relates to the treatment of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

Background art

[0002] NAFLD and NASH

[0003] Non-alcoholic fatty liver disease (NAFLD) is a disorder affecting as many as 1 in 3 - 5 adults and 1 in 10 children in the United States, and refers to conditions where there is an accumulation of excess fat in the liver of people who drink little or no alcohol. The most common form of NAFLD is a non-serious condition called hepatic steatosis (fatty liver), in which fat accumulates in the liver cells: although this is not normal, by itself it probably does not damage the liver. NAFLD most often presents itself in individuals with a constellation of risk factors called the metabolic syndrome, which is characterized by elevated fasting plasma glucose (FPG) with or without intolerance to post-prandial glucose, being overweight or obese, high blood lipids such as cholesterol and triglycerides (TGs) and low high-density lipoprotein cholesterol (HDL-C) levels, and high blood pressure; but not all patients have all the manifestations of the metabolic syndrome. Obesity is thought to be the most common cause of NAFLD; and some experts estimate that about two-thirds of obese adults and one-half of obese children may have fatty liver. The majority of individuals with NAFLD have no symptoms and a normal physical examination (although the liver may be slightly enlarged); children may exhibit symptoms such as abdominal pain and fatigue, and may show patchy dark skin discoloration (acanthosis nigricans). The diagnosis of NAFLD is usually first suspected in an overweight or obese person who is found to have mild elevations in their liver blood tests during routine testing, though NAFLD can be present with normal liver blood tests, or incidentally detected on imaging investigations such as abdominal ultrasound or CT scan. It is confirmed by imaging studies, most commonly a liver ultrasound or magnetic resonance imaging (MRI), and exclusion of other causes.

[0004] Some people with NAFLD may develop a more serious condition called non-alcoholic steatohepatitis (NASH): about 2 – 5% of adult Americans and up to 20% of those who are obese may suffer from NASH. In NASH, fat accumulation in the liver is associated with inflammation and different degrees of scarring. NASH is a potentially serious condition that

carries a substantial risk of progression to end-stage liver disease, cirrhosis and hepatocellular carcinoma. Some patients who develop cirrhosis are at risk of liver failure and may eventually require a liver transplant.

[0005] NAFLD may be differentiated from NASH by the NAFLD Activity Score (NAS), the sum of the histopathology scores of a liver biopsy for steatosis (0 to 3), lobular inflammation (0 to 2), and hepatocellular ballooning (0 to 2). A NAS of <3 corresponds to NAFLD, 3 - 4 corresponds to borderline NASH, and ≥5 corresponds to NASH. The biopsy is also scored for fibrosis (0 to 4).

[0006] NASH is a leading cause of end-stage liver disease; while NAFLD, and to an even greater degree NASH, are intimately related to states of the metabolic syndrome, including insulin resistance (pre-diabetes) and type 2 diabetes mellitus (T2DM), and abdominal obesity. T2DM has been the most prominent predictor for a poor prognosis in NAFLD, whereas elevated liver enzymes are considered unreliable. NASH develops much more frequently in the presence of longstanding T2DM, and the majority of patients with cryptogenic cirrhosis are obese and/or diabetic. Studies have demonstrated that 60% of patients with T2DM and NAFLD had biopsy-proven NASH, and that advanced hepatic fibrosis was present in 75% of those with diabetes and hypertension compared to only 7% without either condition. Haukeland, "Abnormal glucose tolerance is a predictor of nonalcoholic steatohepatitis and fibrosis in patients with non-alcoholic fatty liver disease", *Scand J. Gastroenterol.*, **40**, 1469-1477 (2005), reported that impaired glucose tolerance (IGT) and T2DM were the only independent risk factors for severe NAFLD and NASH, increasing the odds ratio almost 4-fold. Mofrad, "Clinical and histological spectrum of nonalcoholic fatty liver disease associated with normal ALT levels", *Hepatology*, **37**, 1286-1292 (2003), reported a study that demonstrated the lack of predictive value for elevated liver transaminases to diagnose NASH in patients with NAFLD and found T2DM to be the only factor independently associated with an increased risk of advanced fibrosis. Thus, NASH is an overlooked complication of T2DM that is frequently associated with fibrosis and in approximately 10% of patients results in cirrhosis; while the risk of hepatocellular carcinoma is also increased in patients with T2DM and NASH. Patients with NAFLD and NASH usually demonstrate mixed dyslipidemia and the other metabolic derangements described above, including an atherogenic low-density lipoprotein (LDL) phenotype consisting of predominantly of small dense particles. Both metabolic syndrome and NAFLD/NASH are characterized by increased cardiovascular inflammation as measured by elevations in high sensitivity C-reactive protein (hsCRP) and other inflammatory cytokines.

[0007] There is significant worldwide incidence of obesity, metabolic syndrome, pre-diabetes and diabetes, with the prevalence of diabetes worldwide predicted to double to 366 million by 2030. The US population with diabetes has been estimated at 25.4 million (11.5% prevalence) in 2011 and 37.7 million (14.5%) by 2031, with 20.2% of Hispanic adults having diabetes. Because approximately 70% of persons with T2DM have a fatty liver, and the disease follows a more aggressive course with necroinflammation and fibrosis (i.e., NASH) in diabetes, the epidemiology of diabetes suggests significant increases in NASH and chronic liver disease. Using MRI for the noninvasive assessment of hepatic steatosis, the prevalence of NAFLD, when defined as liver fat >5%, has been estimated to be 34% in the USA or approximately 80 million people, and as many as two out of three obese subjects. However, this prevalence is believed to be much higher in T2DM. In a series of 107 unselected patients with T2DM, the prevalence of NAFLD by MRI was 76%, which is similar to recent studies from Italy and Brazil. Recent studies have indicated that the prevalence of NAFLD is rapidly rising in obese children and adolescents, especially those of Hispanic ancestry.

[0008] Treatments for NAFLD and NASH

[0009] There are no drugs currently approved to prevent or treat NAFLD or NASH. A number of pharmacological interventions have been tried in NAFLD/NASH but with overall limited benefit. Antioxidant agents may arrest lipid peroxidation and cytoprotective agents stabilize phospholipid membranes, but agents tried unsuccessfully or with only modest benefit so far include ursodeoxycholic acid, vitamins E (α-tocopherol) and C, and pentoxifylline, among others. Weight-loss agents such as orlistat have had no significant benefit compared to just the use of diet and exercise to achieve weight loss ("weight loss alone"). Most weight-loss studies in NAFLD/NASH have been pilot studies of short duration and limited success, reporting only a modest improvement in necroinflammation or fibrosis. A randomized, double-blind, placebo-controlled 6-month trial (Belfort, "A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis", *N. Engl. J. Med.*, **355**, 2297-2307 (2006)) of weight loss alone against pioglitazone, a thiazolidinedione peroxisome proliferator-activated receptor-γ (PPARγ) agonist and insulin sensitizer, failed to demonstrate any improvement for weight loss alone, but treatment with pioglitazone improved glycemic control, insulin sensitivity, indicators of systemic inflammation (including hsCRP, tumor necrosis factor-α, and transforming growth factor-β), and liver histology in patients with NASH and IGT or T2DM. Treatment with pioglitazone also ameliorated adipose, hepatic, and muscle IR, and was associated with an approximately 50% decrease in necroinflammation ($p < 0.002$) and a 37% reduction in fibrosis

($p = 0.08$). Improvement in hepatocellular injury and fibrosis has been recently reported in another controlled trial with pioglitazone of 12 months duration. In contrast, while the first randomized clinical study with rosiglitazone, the other thiazolidinedione approved for diabetes treatment, in NASH demonstrated a reduction in IR, plasma alanine aminotransferase (ALT) levels and steatosis, rosiglitazone treatment had no significant effect on necrosis, inflammation, or fibrosis. A preliminary report of the 2-year, open-label follow-up of this trial was also disappointing, with no significant benefit from rosiglitazone treatment. Thus, the pharmacological agent with the most robust efficacy in NASH is pioglitazone. Unfortunately, pioglitazone is also associated with a significantly increased risk of weight gain, edema, congestive heart failure, and osteoporotic fractures in both women and men.

[0010] GW510516, a potent peroxisome proliferator-activated receptor-δ (PPARδ) agonist, ameliorated diet-induced obesity and insulin resistance in normal mice, an effect accompanied by enhanced metabolic rate and fatty acid β-oxidation. It also markedly improved diabetes as evidenced by substantial reductions in both glucose and insulin levels in genetically obese *ob/ob* mice. GW510516 has been shown in two Phase 1 studies in healthy subjects to reduce TGs, low-density-lipoprotein cholesterol (LDL-C), apolipoprotein B (apoB), and insulin levels, and improve HDL-C and insulin sensitivity, with one of the studies also showing a 20% reduction in hepatic fat; while a later study confirmed these effects in dyslipidemic subjects with abdominal obesity (reduction in hepatic fat by 20%, 30% decrease in fasting TGs, 26% reduction in apoB, 23% reduction in LDL-C, 40% reduction in fasting non-esterified fatty acids, and 11% decrease in fasting insulin). However, development of GW510516 was discontinued after observations in animal studies of its association with the rapid development of cancers in several organs.

[0011] The dual peroxisome proliferator-activated receptor-α/peroxisome proliferator-activated receptor-δ (PPARα/δ) agonist GFT505 has preferential α ($EC_{50} = 6$ nM) and secondary δ ($EC_{50} = 47$ nM) agonist activity. The lipid-modifying efficacy of GFT505 has been confirmed in both healthy subjects, as well as in patients with T2DM, combined abdominal obesity and mixed dyslipidemia, combined abdominal obesity and pre-diabetes, atherogenic dyslipidemia, and insulin resistance. These effects include reduction in TGs, non-HDL-C, and total cholesterol, LDL-C, and apoB; and increases in HDL-C. Preclinical studies in rodent models of NAFLD/NASH demonstrated that GFT505 treatment decreased hepatic steatosis, inflammation, and fibrosis, and decreased liver dysfunction markers; while in clinical studies GFT505 has been reported to decrease a range of liver dysfunction markers including ALT,

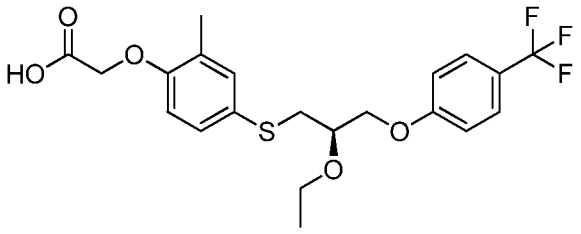
alkaline phosphatase (ALP), and γ-glutamyl transferase (GGT). A 1-year liver biopsy-based Phase2b trial in NASH initially recruited patients for treatment with 80 mg/day of GFT505 or placebo, with an interim safety analysis at 6 months showing no safety issue that compromised the ongoing study; and a second recruitment phase has selected patients for treatment with 120 mg/day of GFT505 or placebo.

[0012] Obeticholic acid (OCA, 6α-ethylchenodeoxycholic acid), a semi-synthetic bile acid analog that is a highly potent farnesoid X receptor agonist, was studied in a Phase 2 study for NASH, the FLINT study, sponsored by the US National Institute of Diabetes and Digestive and Kidney Diseases. That study was halted early in January 2014, after about half of the 283 subjects had completed the study, when a planned interim analysis showed that the primary endpoint had been met. The treatment (OCA 25mg/day for 72 weeks) resulted in a highly statistically significant improvement ($p = 0.0024$ on an intention-to-treat basis, compared to placebo) in the primary histological endpoint, defined as a decrease in NAS of at least two points with no worsening of fibrosis.

[0013] Notwithstanding the initial benefits reported for GFT505 and OCA, there still remains a significant unmet clinical need for an effective and well-tolerated drug that can prevent or slow down the progression of NAFLD and NASH.

[0014] MBX-8025

[0015] MBX-8025 is the compound of the formula



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MBX-8025 has the chemical name *(R)*-2-(4-((2-ethoxy-3-(4-(trifluoromethyl)phenoxy)propyl)-thio)-2-methylphenoxy)acetic acid [IUPAC name as generated by CHEMDRAW ULTRA 12.0]. MBX-8025 and its synthesis, formulation, and use is disclosed in, for example, US Patent No. 7301050 (compound 15 in Table 1, Example M, claim 49), US Patent No. 7635718 (compound 15 in Table 1, Example M), and US Patent No. 8106095 (compound 15 in Table 1, Example M, claim 14). Lysine (L-lysine) salts of MBX-8025 and related compounds are disclosed in US Patent No. 7709682 (MBX-8025 L-lysine salt throughout the Examples, crystalline forms claimed).

[0016] MBX-8025 is an orally active, potent (2 nM) agonist of PPARδ, It is specific (>600-fold and >2500-fold compared with PPARα and PPARγ receptors). PPARδ activation stimulates fatty acid oxidation and utilization, improves plasma lipid and lipoprotein metabolism, glucose utilization, and mitochondrial respiration, and preserves stem cell homeostasis. According to US Patent No. 7301050, PPARδ agonists, such as MBX-8025, are suggested to treat PPARδ-mediated conditions, including "diabetes, cardiovascular diseases, Metabolic X syndrome, hypercholesterolemia, hypo-HDL-cholesterolemia, hyper-LDL-cholesterolemia, dyslipidemia, atherosclerosis, and obesity", with dyslipidemia said to include hypertriglyceridemia and mixed hyperlipidemia.

[0017] A Phase 2 study of MBX-8025 L-lysine dihydrate salt in mixed dyslipidemia (6 groups, 30 subjects/group: once daily placebo, atorvastatin (ATV) 20 mg, or MBX-8025 L-lysine dihydrate salt at 50 or 100 mg (calculated as the free acid) capsules alone or combined with ATV 20 mg, for 8 weeks) has been reported by Bays et al., "MBX-8025, A Novel Peroxisome Proliferator Receptor-δ Agonist: Lipid and Other Metabolic Effects in Dyslipidemic Overweight Patients Treated with and without Atorvastatin", *J. Clin. Endocrin. Metab.*, **96**(9), 2889-2897 (2011) and Choi et al., "Effects of the PPAR-δ agonist MBX-8025 on atherogenic dyslipidemia", *Atherosclerosis*, **220**, 470-476 (2012). Compared to placebo, MBX-8025 alone and in combination with atorvastatin significantly ($P < 0.05$) reduced apoB100 by 20-38%, LDL by 18-43%, triglycerides by 26-30%, non-HDL-C by 18–41%, free fatty acids by 16-28%, and high-sensitivity C-reactive protein by 43-72%; it raised HDL-C by 1-12% and also reduced the number of patients with the metabolic syndrome and a preponderance of small LDL particles. While MBX-8025 at 100 mg/day reduced LDL-C by 22% over the total population treated, the percentage reduction in LDL-C increased to 35% in the tertile with the highest starting LDL-C levels (187-205 mg/dL), and trend analysis on individual patient data confirmed a positive correlation between percentage reduction in LDL-C and starting LDL-C level. MBX-8025 reduced LDL-S/VS by 40-48% compared with a 25% decrease with atorvastatin; and MBX-8025 increased LDL-L by 34-44% compared with a 30% decrease with atorvastatin. MBX-8025 significantly reduced alkaline phosphatase by 32-43%, compared to reductions of only 4% in the control group and 6% in the ATV group; and significantly reduced γ-glutamyl transpeptidase by 24-28%, compared to a reduction of only 3% in the control group and an increase of 2% in the ATV group. Thus MBX-8025 corrects all three lipid abnormalities in mixed dyslipidemia: lowers TGs and LDL and raises HDL, selectively depletes small dense LDL particles (92%), reduces cardiovascular

inflammation, and improves other metabolic parameters: increases insulin sensitivity (lowers HOMA-IR, fasting plasma glucose, and insulin), lowers γ-glutamyl transpeptidase and alkaline phosphatase, significantly (>2-fold) reduces the percentage of subjects meeting the criteria for metabolic syndrome, and trends towards a decrease in waist circumference and increase in lean body mass. pattern I to pattern A; and from pattern B to pattern I or A, where LDL particle size pattern B is a predominant LDL particle size of less than 25.75 nm, pattern I is a predominant LDL particle size of from 25.75 nm to 26.34 nm, and pattern A is a predominant LDL particle size of greater than 26.34 nm, where the LDL particle size is measured by gradient-gel electrophoresis.

Summary of the invention

[0018] This invention is the treatment of NAFLD and NASH, comprising therapy with MBX-8025 or an MBX-8025 salt.

[0019] Because MBX-8025 effectively enhances fatty acid β-oxidation and lowers serum apoB, LDL-C, TGs, non-esterified fatty acids, and hsCRP in clinical and in non-clinical studies, while raising HDL-C in humans, its use will be effective in the treatment of NAFLD and NASH. Further, unlike fenofibrate, MBX-8025 will significantly decrease hepatic fat (assessed by MRI), reduce transaminases, multiple inflammatory cytokines, the hepatocellular apoptosis marker CK18, improve the LDL phenotype, and demonstrate improvement in multiple glycemic parameters including glycated hemoglobin (HbA1c), FPG, fasting insulin, and HOMA-IR. Because the presence of >6% hepatic fat content by MRI in obese subjects with insulin resistance is very predictive of both NAFLD and NASH, reduction of hepatic fat by treatment with MBX-8025 will be significant in the treatment of NAFLD and NASH.

[0020] In various aspects, this invention is:
a method of treating NAFLD or NASH by administering MBX-8025 or an MBX-8025 salt;
MBX-8025 or an MBX-8025 salt for use in treating NAFLD or NASH;
the use of MBX-8025 or an MBX-8025 salt for treating NAFLD or NASH, or in the manufacture of a medicament for treating NAFLD or NASH;
pharmaceutical compositions for treating NAFLD or NASH comprising MBX-8025 or an MBX-8025 salt; and
kits for treating NAFLD or NASH comprising compositions comprising MBX-8025 or an MBX-8025 salt.

[0021] Preferred embodiments of this invention are characterized by the specification and by the features of Claims 1 to 12 of this application as filed.

Detailed description of the invention

[0022] Definitions

[0023] "NAFLD" and "NASH" and their treatment are described in paragraphs [0002] through [0012].

[0024] A "therapeutically effective amount" of MBX-8025 or an MBX-8025 salt means that amount which, when administered to a human for treating NAFLD or NASH, is sufficient to effect treatment for the NAFLD or NASH. "Treating" or "treatment" of NAFLD or NASH in a human includes one or more of:

(1) preventing or reducing the risk of developing NAFLD or NASH, i.e., causing the clinical symptoms of NAFLD or NASH not to develop in a subject who may be predisposed to NAFLD or NASH but who does not yet experience or display symptoms of the NAFLD or NASH (i.e. prophylaxis);

(2) inhibiting NAFLD or NASH, i.e., arresting or reducing the development of NAFLD or NASH or its clinical symptoms; and

(3) relieving NAFLD or NASH, i.e., causing regression, reversal, or amelioration of the NAFLD or NASH or reducing the number, frequency, duration or severity of its clinical symptoms.

The therapeutically effective amount for a particular subject varies depending upon the health and physical condition of the subject to be treated, the extent of the NAFLD or NASH, the assessment of the medical situation, and other relevant factors. It is expected that the therapeutically effective amount will fall in a relatively broad range that can be determined through routine trial.

[0025] "MBX-8025" is described in paragraphs [0014] through [0017].

[0026] Salts (for example, pharmaceutically acceptable salts) of MBX-8025 are included in this invention and are useful in the compositions, methods, and uses described in this application. These salts are preferably formed with pharmaceutically acceptable acids. See, for example, "Handbook of Pharmaceutically Acceptable Salts", Stahl and Wermuth, eds., Verlag Helvetica Chimica Acta, Zürich, Switzerland, for an extensive discussion of pharmaceutical

salts, their selection, preparation, and use. Unless the context requires otherwise, reference to MBX-8025 is a reference both to the compound and to its salts.

[0027] Because MBX-8025 contains a carboxyl group, it may form salts when the acidic proton present reacts with inorganic or organic bases. Typically the MBX-8025 is treated with an excess of an alkaline reagent, such as hydroxide, carbonate or alkoxide, containing an appropriate cation. Cations such as Na^+, K^+, Ca^{2+}, Mg^{2+}, and NH_4^+ are examples of cations present in pharmaceutically acceptable salts. Suitable inorganic bases, therefore, include calcium hydroxide, potassium hydroxide, sodium carbonate and sodium hydroxide. Salts may also be prepared using organic bases, such as salts of primary, secondary and tertiary amines, substituted amines including naturally-occurring substituted amines, and cyclic amines including isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, *N*-alkylglucamines, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, and the like. As noted in paragraph [0017], MBX-8025 is currently formulated as its L-lysine dihydrate salt; and MBX-8025 has also been studied in clinical trials as its calcium salt.

[0028] "Comprising" or "containing" and their grammatical variants are words of inclusion and not of limitation and mean to specify the presence of stated components, groups, steps, and the like but not to exclude the presence or addition of other components, groups, steps, and the like. Thus "comprising" does not mean "consisting of", "consisting substantially of", or "consisting only of"; and, for example, a formulation "comprising" a compound must contain that compound but also may contain other active ingredients and/or excipients.

[0029] Formulation and administration

[0030] The MBX-8025 may be administered by any route suitable to the subject being treated and the nature of the subject's condition. Routes of administration include administration by injection, including intravenous, intraperitoneal, intramuscular, and subcutaneous injection, by transmucosal or transdermal delivery, through topical applications, nasal spray, suppository and the like or may be administered orally. Formulations may optionally be liposomal formulations, emulsions, formulations designed to administer the drug across mucosal membranes or transdermal formulations. Suitable formulations for each of these methods of administration may be found, for example, in "Remington: The Science and Practice of Pharmacy", 20th ed., Gennaro, ed., Lippincott Williams & Wilkins, Philadelphia, Pa., U.S.A. Because MBX-8025 is

orally available, typical formulations will be oral, and typical dosage forms will be tablets or capsules for oral administration. As mentioned in paragraph [0017], MBX-8025 has been formulated in capsules for clinical trials.

[0031] Depending on the intended mode of administration, the pharmaceutical compositions may be in the form of solid, semi-solid or liquid dosage forms, preferably in unit dosage form suitable for single administration of a precise dosage. In addition to an effective amount of the MBX-8025, the compositions may contain suitable pharmaceutically-acceptable excipients, including adjuvants which facilitate processing of the active compounds into preparations which can be used pharmaceutically. "Pharmaceutically acceptable excipient" refers to an excipient or mixture of excipients which does not interfere with the effectiveness of the biological activity of the active compound(s) and which is not toxic or otherwise undesirable to the subject to which it is administered.

[0032] For solid compositions, conventional excipients include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talc, cellulose, glucose, sucrose, magnesium carbonate, and the like. Liquid pharmacologically administrable compositions can, for example, be prepared by dissolving, dispersing, etc., an active compound as described herein and optional pharmaceutical adjuvants in water or an aqueous excipient, such as, for example, water, saline, aqueous dextrose, and the like, to form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary excipients such as wetting or emulsifying agents, pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, etc.

[0033] For oral administration, the composition will generally take the form of a tablet or capsule, or it may be an aqueous or nonaqueous solution, suspension or syrup. Tablets and capsules are preferred oral administration forms. Tablets and capsules for oral use will generally include one or more commonly used excipients such as lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. When liquid suspensions are used, the active agent may be combined with emulsifying and suspending excipients. If desired, flavoring, coloring and/or sweetening agents may be added as well. Other optional excipients for incorporation into an oral formulation include preservatives, suspending agents, thickening agents, and the like.

[0034] Typically, a pharmaceutical composition of MBX-8025, or a kit comprising compositions of MBX-8025, is packaged in a container with a label, or instructions, or both, indicating use of the pharmaceutical composition or kit in the treatment of NAFLD and/or NASH.

[0035] A suitable amount of MBX-8025 (calculated as the free acid) for oral dosing will be 20-200 mg/day, preferably 50-100 mg/day, for an adult subject with NAFLD or NASH. That is, a suitable amount of MBX-8025 for oral dosing will be similar to the amounts employed in clinical trials; though it is possible that the therapeutically effective amount may be higher in severe cases of NAFLD or NASH. Suitable reductions in dose toward the lower end of the outer range above will be made for subjects who are children, depending on such additional factors as age and body mass.

[0036] A person of ordinary skill in the art of the treatment of NAFLD or NASH will be able to ascertain a therapeutically effective amount of the MBX-8025 or an MBX-8025 salt for a particular stage of disease to achieve a therapeutically effective amount without undue experimentation and in reliance upon personal knowledge and the disclosure of this application.

[0037] Example

[0038] Subjects with NAFLD or NASH are treated with doses of either 50 or 100 mg/day of MBX-8025 for 6 months. Subjects are permitted their usual other medications (e.g. antidiabetic medications such as metformin or sulfonamides) but not glitazones, PPAR agonists, OCA, or similar medications. The subjects are assessed before the study, and at intervals during the study, such as every 4 weeks during the study and 4 weeks after the last dose of the MBX-8025 therapy, for safety and pharmacodynamic evaluations. MRIs of the subjects' livers are taken every 4 weeks during the study and 4 weeks after completion of MBX-8025 dosing, to determine hepatic fat; and liver biopsies are taken before the study (to establish the diagnosis) and 4 weeks after completion of MBX-8025 dosing. At each visit, after a 12-hour fast, blood is drawn and urine collected; and a standard metabolic panel, complete blood count, and standard urinalysis are performed. Blood is analyzed for total cholesterol, HDL-C, LDL-C, VLDL-C, TGs, apoB, and liver transaminases. The subjects also maintain health diaries, which are reviewed at each visit. The subjects show a dose-related improvement in their disease, as manifested by, for example, MRI and liver biopsy.

Claims:

1. The use of a compound that is *(R)*-2-(4-((2-ethoxy-3-(4-(trifluoromethyl)phenoxy)-propyl)thio)-2-methylphenoxy)acetic acid or a salt thereof for the manufacture of a medicament for treating a condition that is non-alcoholic fatty liver disease or non-alcoholic steatohepatitis.

2. The use of claim 1 where the compound is *(R)*-2-(4-((2-ethoxy-3-(4-(trifluoromethyl)-phenoxy)propyl)thio)-2-methylphenoxy)acetic acid l-lysine dihydrate salt.

3. The use of claim 1 or 2 where the medicament is for oral administration.

4. The use of any one of claims 1 to 3 where the daily dose of the compound is 20-200 mg when the dose of the compound is calculated as *(R)*-2-(4-((2-ethoxy-3-(4-(trifluoromethyl)phenoxy)propyl)thio)-2-methylphenoxy)acetic acid.

5. The use of claim 4 wherein the daily dose of the compound is 50-100 mg when the dose of the compound is calculated as *(R)*-2-(4-((2-ethoxy-3-(4-(trifluoromethyl)phenoxy)propyl)thio)-2-methylphenoxy)acetic acid.

6. The use of any one of claims 1 to 5 wherein the medicament is to be administered once/day.

7. The use of any one of claims 1 to 6 wherein the condition is non-alcoholic fatty liver disease.

8. The use of any one of claims 1 to 6 wherein the condition is non-alcoholic steatohepatitis.