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(54) **COMPOSITIONS AND METHODS FOR TREATING NON-ALCOHOLIC STEATOHEPATITIS**

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(57) **ABSTRACT**

Compositions and method are disclosed comprising ethyl icosapentate for use in treatment of non-alcoholic steatohepatitis (NASH).

COMPOSITIONS AND METHODS FOR TREATING NON-ALCOHOLIC STEATOHEPATITIS

TECHNICAL FIELD

[0001] The present invention relates to compositions and methods comprising ethyl icosapentate for treatment of non-alcoholic steatohepatitis (NASH).

BACKGROUND ART

[0002] It is known that heavy alcohol use can lead to liver complications, including alcoholic hepatitis which is often characterized by fatty liver and inflammation. Alcoholic hepatitis can ultimately lead to cirrhosis of the liver (scarring) and hardening of the liver tissue.

[0003] Individuals that do not consume excessive amounts of alcohol can also be found to have liver disease complications. Non-alcoholic fatty liver disease (NAFLD) is understood to encompass a variety of liver diseases, including steatosis (simple fatty liver), non-alcoholic steatohepatitis (NASH) and advanced scarring of the liver (cirrhosis). NASH has traditionally been diagnosed by means of a liver biopsy to characterize the liver histology, particularly with respect to the characteristics of inflammation, fibrosis and steatosis (fat accumulation). NASH then generally prefers to clinical findings based upon the liver biopsy of a patient with steatohepatitis, combined with the absence of significant alcohol consumption (Neuschwander-Tetri, B. A. and S. H. Caldwell (2003) Hepatology 37(5): 1202-1209). In NASH, fat accumulation is seen in varying degrees of inflammation (hepatitis) and scarring (fibrosis). Patients having NASH are also often characterized by abnormal levels of liver enzymes, such as aspartate aminotransferase (AST, GOT) and alanine aminotransferase (ALT, GPT). However, a clinical diagnosis of NASH still depends upon a liver biopsy to assess the histologic characteristics of the patient's liver, such that histological examination of liver biopsy tissue is often characterized as the "gold-standard" technique for the assessment of liver fibrosis (Neuschwander-Tetri, ibid).

CITATION LIST

Non Patent Literature

[0004] Non Patent Literature 1; Hepatology June 2005; 41:1313-1321 "Design and validation of a historical scoring system for nonalcoholic fatty liver disease"

SUMMARY OF INVENTION

Technical Problem

[0005] The object of the present invention is to provide the compositions and methods comprising ethyl icosapentate for the treatment or alleviation of non-alcoholic steato-hepatitis (NASH), and alleviation of the symptoms associated with NASH.

Solution to Problem

[0006] In one embodiment of the invention is that a pharmaceutical agent for treatment or alleviation of symptoms of non-alcoholic steatohepatitis (hereinafter abbreviated as NASH), an effective amount of ethyl icosapentate is administered.after determining in a subject a baseline level indicative of NASH of at least one criteria selected from the group consisting of NAS score, steatosis score, lobular inflammation score, ballooning score and fibrosis stage.

[0007] In (1) embodiment of the invention Ethyl icosapentate for use in the treatment or alleviation of symptoms of NASH in a subject in need thereof, wherein:

[0008] (a) a baseline level in a subject having NASH of at least one criteria selected from the group consisting of NAS score, steatosis score, lobular inflammation score, ballooning score and fibrosis stage is determined; and

[0009] (b) an effective amount of ethyl icosapentate (EPA-E) is administered to said subject.

[0010] (2) The ethyl icosapentate for use of (1), wherein said subject has a NAS score of 4 or more than 4.

[0011] (3) The ethyl icosapentate for use (1) or (2), wherein said subject is characterized by at least one criteria selected from the group consisting of a baseline ALT value of 10 to 300 U/L; a baseline AST value of 10 to 250 U/L; a baseline steatosis grade of 2 to 3; and a baseline lobular inflammation grade of 2 to 3.

[0012] (4) The ethyl icosapentate for use of any one of (1) to (3), wherein after said administration of said EPA-E for about one year, said subject exhibits at least one improvement selected from the group consisting of a reduced ALT value as compared to said baseline ALT value; a reduced AST value as compared to said baseline AST value; a reduced steatosis grade as compared to said baseline steatosis grade; and a reduced lobular inflammation grade as compared to said baseline lobular inflammation grade.

[0013] (5) The ethyl icosapentate for use of any one of (1) to (4), wherein said ethyl icosapentate is administered to said subject in an amount of between 300 to 4000 mg per day.

[0014] (6) The ethyl icosapentate for use of any one of (1) to (5), wherein said subject is further characterized by having at least one condition selected from the group consisting of high TG, low HDL-C, diabetes, impaired glucose tolerance and metabolic syndrome.

[0015] (7) The ethyl icosapentate for use of any one of (4) to (6), wherein said reduced ALT value is at least 5% lower than said baseline ALT value and/or said reduced AST value is at least 5% lower than said baseline AST value.

[0016] (8) The ethyl icosapentate for use of any one of (1) to (7), further comprising determining in said subject prior to treatment a baseline level in serum of at least one member selected from the group consisting of ALT in a range of 10 to 300 U/L, AST in a range of 10 to 250 U/L, HDL-C in a range of 25 to 55 mg/dl, LDL-C in a range of 100 to 200 mg/dl, triglycerides in a range of 100 to 1000 mg/dl, TC in a range of 170 to 300 mg/dl, High TG and low HDL-C, TG/HDL-C ratio in a range of 3.75 to 10, non-HDL-C in a range of 100 to 250 mg/dl, Free fatty acid in a range of 400 to 1000 micro Eq/L, HOMA-IR in a range of 1.5 to 5, HbA1c in a range of 5.7 to 10%, Fasting plasma glucose in a range of 100 to 200 mg/dl.

[0017] (9) The ethyl icosapentate for use of any one of (1) to (8), wherein after administration of ethyl icosapentate for at least 3 months, said subject exhibits the following changes in said at least one marker as compared to the baseline level of at least 1% reduction for ALT, AST, TG, TG/HDL ratio, Free fatty acid, AA, MUFA, Palmitoleic acid, Oleic acid, Oleic acid/Stearic acid ratio, Palmitoleic acid/Palmitic acid ratio, Adrenic acid/AA ratio, Ferritin, Thioredoxin, TNF-alpha, sTNF-R1, sTNF-R2, Hs-CRP, CRGF, sCD40, Leptin, complement factor D, CK18 fragment, serum HMGB1, soluble Fas antigen, Hyaluronic acid, Type IV collagen (7s

domain), procollagen III peptide or PAI-1; at least 5% increase for EPA or EPA/AA ratio; at least 1% increase for DPA, AA/Homo-gamma-linolenic acid ratio or Serum adiponectin; no worsening of ALP, bilirubin, GGT, Albumin, HDL-C, LDL-C, TC, non-HDL-C, HOMA-IR, HbAp1c, Glucose, Fasting plasma glucose, postprandial plasma glucose, OGTT, platelet count or BMI.

[0018] (10) The ethyl icosapentate for use of any one of (1) to (9), wherein: the NAS score in said subject after administering (i) to a composite score of 3 or less than 3 and no worsening of said fibrosis stage score, or (ii) by 2 or more than 2 across at least two of the NAS components and no worsening of said fibrosis stage score is improved.

[0019] In another embodiment of the invention the ethyl icosapentate for use in the treatment or alleviation of symptoms of NASH, wherein an effective amount of ethyl icosapentate is administered to a subject for treating NASH after identifying the subject having NASH; determining the baseline level in the subject of at least one criteria selected from the group consisting of NAS score, steatosis score, lobular inflammation score, ballooning score and fibrosis stage.

[0020] In another embodiment of the invention ethyl icosapentate for use in the treatment or alleviation of symptoms of NASH, wherein a subject/patient having NASH is identified after determining the baseline level in the subject of at least one criteria selected from the group consisting of NAS score, steatosis score, lobular inflammation score, ballooning score and fibrosis stage; administering to the subject an effective amount of ethyl icosapentate; and improving the NAS score (i) to a composite score of less than 3 or equal to 3 or (ii) by 2 across at least two of the NAS components, combined with no worsening of the fibrosis stage score.

[0021] In another embodiment of the invention the ethyl icosapentate for use in treatment or alleviation of symptoms NASH, wherein the identification is a subject having NASH characterized by baseline levels of ALT of between 5 to 300 U/L and at least one criteria selected from the group consisting of NAS score of 4 or more than 4, a steatosis score of 1 or more than 1, a lobular inflammation score of 1 or more than 1 and either (i) a fibrosis stage of at least 1a or (ii) ballooning; administering to the subject an effective amount of ethyl icosapentate; and improving the NAS score in the subject (i) to a composite score of 3 or less than 3 or (ii) by 2 or more than 2 across at least two of the NAS components, together with no worsening of the fibrosis stage score.

[0022] In another embodiment of the invention, the ethyl icosapentate for use in treatment or alleviation of symptoms NASH, wherein;

[0023] a subject is identified having NASH characterized by baseline levels of ALT of between 5 to 300 U/L and at least one criteria selected from the group consisting of NAS score of 4 or more than 4, a steatosis score of 1 or more than 1, a lobular inflammation score of 1 or more than 1 and either (i) a fibrosis stage of at least 1a or (ii) ballooning, and at least one or any combination of two or more of the pretreatment baseline of the items mentioned in Tables 1 and 2;

[0024] a baseline level in blood or physical condition prior to treatment in the subject is determined;

[0025] an effective amount of ethyl icosapentate is administered to the subject; and the NAS score in the subject (i) to a composite score of 3 or less than 3, or (ii)

[0026] by 2 or more than 2 across at least two of the NAS components, together with no worsening of the fibrosis stage

score, optionally improving at least one selected from the items mentioned in Tables 1 and 2 is improved.

[0027] In another embodiment of the invention, the ethyl icosapentate for use in treatment or alleviation of symptoms NASH, wherein the subject is taking at least one drug selected from the group consisting of lipid-lowering drugs, HMG-CoA reductase inhibitors (stains), fibrates, probucol, ezetimibe, ursodiol (UDCA), taurine, betaine, N-acetylcysteine, s-adenosylmethionine (SAM-e), milk thistle, anti-TUMOR NECROSIS FACTOR (TNF) therapies, probiotics, anti-diabetic medications, biguanides (metformin), insulin, sulfonylureas, alpha-glucosidase inhibitors (acarbose), dipeptidyl-peptidase 4 inhibitors (sitagliptin, saxagliptin, alogliptin, vildagliptin, linagliptin, etc.), phenylalanine derivatives (nateglinide, repaglinide), anti-platelet therapy, anti-thrombotic agents, Glucagon-like peptide-1(GLP-1) receptor agonists (liraglutide, exenatide, taspoglutide, etc.), PDE-4 inhibitor, angiotensin II-1 type receptor antagonist (ARB: losartan, etc.), polyenephosphatidylcholine, antioxidant (vitamine E, vitamin C, nicotinic acid tocopherol,etc.), and pentoxifylline.

[0028] In another embodiment of the invention, ethyl icosapentate for use in the treatment or alleviation of symptoms of NASH wherein,

[0029] a subject is identified having NASH characterized by baseline levels of ALT of between 5 to 300 U/L and at least one criteria selected from the group consisting of NAS score of 4 or more than 4, a steatosis score of 1 or more than 1, a lobular inflammation score of 1 or more than 1 and either (i) a fibrosis stage of at least 1a or (ii) ballooning, and at least one or any combination of two or more of the pretreatment baseline of the items mentioned in Tables 1 and 2;

[0030] a baseline level in blood or physical condition prior to treatment in the subject is determined;

[0031] an effective amount of ethyl icosapentate administering to the subject in combination with at least one drug selected from the group consisting of lipid-lowering drugs, HMG-CoA reductase inhibitors (stains), fibrates, probucol, ezetimibe, ursodiol (UDCA), taurine, betaine, N-acetylcysteine, s-adenosylmethionine (SAM-e), milk thistle, anti-TNF therapies, probiotics, anti-diabetic medications: biguanides (metformin), insulin, sulfonylureas, alpha-glucosidase inhibitors (acarbose), dipeptidyl-peptidase 4 inhibitors (sitagliptin, saxagliptin, alogliptin, vildagliptin, linagliptin, etc.), phenylalanine derivatives (nateglinide, repaglinide), anti-platelet therapy, anti-thrombotic agents, Glucagon-like peptide-1(GLP-1) receptor agonists (liraglutide, exenatide, taspoglutide, etc.), PDE-4 inhibitor, angiotensin II-1 type receptor antagonist (ARB: losartan, etc.), polyenephosphatidylcholine, antioxidant (vitamine E, vitamin C, nicotinic acid tocopherol,etc.), and pentoxifylline; and

[0032] the NAS score in the subject is improved (i) to a composite score of 3 or less than 3, or (ii) by 2 or more than 2 across at least two of the NAS components, together with no worsening of the fibrosis stage score, optionally improving at least one of items mentioned in Tables 1 and 2.

[0033] In a further embodiment of the invention, ethyl icosapentate for use in the treatment or alleviation of symptoms of NASH wherein a subject an effective amount of ethyl icosapentate is administered, the subject has NASH characterized by baseline levels of ALT of between 5 to 300 U/L and at least one criteria selected from the group consisting of a NAS score of 4 or more than 4, a steatosis score of 1 or more than 1, lobular inflammation score of 1 or more than 1 and

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either (i) a fibrosis stage of at least la or (ii) ballooning; and the NAS score in the subject (i) to a composite score of 3 or less than 3, or (ii) by 2 or more than 2 across at least two of the NAS components, together with no worsening of the fibrosis stage score is improved.

[0034] In another embodiment of the invention, ethyl icosapentate for use in reducing steatosis, liver lobular inflammation, ballooning and/or liver fibrosis in a subject in need thereof, wherein, an effective amount of ethyl icosapentate (EPA-E) is administered to a subject; at least one condition selected from the group consisting of the steatosis, lobular inflammation, ballooning and liver fibrosis condition of said subject is improved, and no worsening of said fibrosis stage score; and said subject exhibits the following changes in said at least one marker as compared to a baseline pretreatment level of at least 1% reduction for ALT, AST, Triglycerides (TG), TG/HDL-C ratio, Free fatty acid, Arachidonic acid (AA), monounsaturated fatty acid (MUFA), Palmitoleic acid, Oleic acid, Oleic Acid/Stearic acid ratio, Palmitoleic acid/ Palmitic acid ratio, Stearic acid/Palmitic acid ratio, gamma-linolenic acid/Linolenic acid ratio, Adrenic acid/AA ratio, Ferritin, Thioredoxin, Tumor necrosis factor-alpha (TNF-alpha), sTNF-R1(Tumor necrosis factor receptor I, soluble), sTNF-R2(Tumor necrosis factor receptor II, soluble), Hs-CRP, CTGF, sCD40, Leptin, complement factor D, CK18 fragment, serum HMGB1, soluble Fas antigen, Hyaluronic acid, Type IV collagen (7s domain), procollagen III peptide or PAI-1; at least 5% increase for EPA or EPA/AA ratio; at least 1% increase for DPA, AA/Homo-gamma-linolenic acid ratio or Serum adiponectin; no worsening of ALP, bilirubin, GGT, Albumin, HDL-C, LDL-C, Total Cholesterol (TC), non-HDL-C, HOMA-IR, HbA1c, Fasting plasma glucose, post-prandial plasma glucose, OGTT, platelet count or BMI.

[0035] In another embodiment of the invention, the ethyl icosapentate for use in reducing steatosis, liver lobular inflammation, ballooning and/or liver fibrosis in a subject in need thereof, wherein;

[0036] a baseline level in blood or physical condition prior to treatment in the subject having at least one item or any combination of two or more items selected from the pretreatment baseline of the items mentioned in Tables 1 and 2 is determined;

[0037] an effective amount of ethyl icosapentate (EPA-E) is administered to the subject;

[0038] at least one condition selected from the group consisting of the steatosis, lobular inflammation, ballooning and liver fibrosis condition of said subject without worsening said fibrosis stage score is improved; and

[0039] said subject exhibits the described changes in at least one of items mentioned in Tables 1 and 2 as compared to a baseline pre-treatment level of the item.

[0040] In another embodiment of the invention, the ethyl icosapentate for use in treatment or alleviation of symptoms NASH, wherein the subject is taking at least one drug selected from the group consisting of lipid-lowering drugs, HMG-CoA reductase inhibitors (stains), fibrates, probucol, ezetimibe, ursodiol (UDCA), taurine, betaine, N-acetylcysteine, s-adenosylmethionine (SAM-e), milk thistle, anti-TNF therapies, probiotics, anti-diabetic medications: biguanides (metformin), insulin, sulfonylureas, alpha-glucosidase inhibitors (acarbose), dipeptidyl-peptidase 4 inhibitors (sitagliptin, saxagliptin, alogliptin, vildagliptin, linagliptin, etc.), phenylalanine derivatives (nateglinide, repaglinide), anti-platelet therapy, anti-thrombotic agents, Glucagon-like pep-

tide-1(GLP-1) receptor agonists (liraglutide, exenatide, taspoglutide, etc.), PDE-4 inhibitor, angiotensin II-1 type receptor antagonist (ARB: losartan, etc.), polyenephosphatidylcholine, antioxidant (vitamine E, vitamin C, nicotinic acid tocopherol,etc.), and pentoxifylline.

[0041] In another embodiment of the invention, ethyl icosapentate for use in the treatment or alleviation of symptoms of NASH wherein an effective amount of ethyl icosapentate is administered to a subject, wherein the subject is possible or definite NASH, and a baseline level in blood or physical condition prior to treatment in the subject of at least one member selected from the group consisting of ALT, AST, AST/ALT ratio, ALP, bilirubin, GGT, Albumin, HDL-C, LDL-C, TG, TC, TG/HDL-C ratio, non-HDL-C, Free fatty acid, AA, EPA, DPA, DHA, EPA/AA ratio, DPA/AA ratio, DHA/AA ratio, DHA/DPA ratio, MUFA, Palmitoleic acid, Oleic acid, Oleic acid/Stearic acid ratio, Palmitoleic acid/ Palmitic acid ratio, Stearic acid/Palmitic acid ratio, gamma-linolenic acid/Linolenic acid ratio, AA/Homo-gamma-lino-lenic acid ratio, Adrenic acid/AA ratio, Ferritin, Thioredoxin, TNF-alpha, sTNF-R1, sTNF-R2, Hs-CRP, CTGF, sCD40, HOMA-IR, HbA1c, Glucose, Fasting plasma glucose, post-prandial plasma glucose, OGTT, Leptin, Serum adiponectin, complement factor D, CK18 fragment, serum HMGB1, soluble Fas antigen, Hyaluronic acid, Type IV collagen (7s domain), pro-collagen III peptide, PAI-1, platelet count or BMI is determined.

[0042] In another embodiment of the invention, the ethyl icosapentate for use in the treatment or alleviation of symptoms of NASH, wherein the subject is possible or definite NASH and an effective amount of ethyl icosapentate is administered to a subject, wherein a baseline level in blood or physical condition prior to treatment in the subject of at least one item or any combination of two or more items selected from the items mentioned in Tables 1 and 2 is determined.

[0043] In another embodiment of the invention, the ethyl icosapentate for use in treatment or alleviation of symptoms NASH, wherein the subject is possible or definite NASH and the subject is taking at least one drug selected from the group consisting of lipid-lowering drugs, HMG-CoA reductase inhibitors (stains), fibrates, probucol, ezetimibe, ursodiol (UDCA), taurine, betaine, N-acetylcysteine, s-adenosylme-thionine (SAM-e), milk thistle, anti-TNF therapies, probiotics, anti-diabetic medications: biguanides (metformin), insulin, sulfonylureas, alpha-glucosidase inhibitors (acarbose), dipeptidyl-peptidase 4 inhibitors (sitagliptin, saxagliptin, alogliptin, vildagliptin, linagliptin, etc.), phenylalanine derivatives (nateglinide, repaglinide), anti-platelet therapy, anti-thrombotic agents, Glucagon-like peptide-1(GLP-1) receptor agonists (liraglutide, exenatide, taspoglutide, etc.), PDE-4 inhibitor, angiotensin II-1 type receptor antagonist (ARB: losartan, etc.), polyenephosphatidylcholine, antioxidant (vitamine E, vitamin C, nicotinic acid tocopherol,etc.), and pentoxifylline.

[0044] In another embodiment of the invention, the ethyl icosapentate for use in the treatment or alleviation of symptoms of NASH wherein an effective amount of ethyl icosapentate is administered to a subject, wherein the subject is possible or definite NASH, and exhibits the following changes in said at least one marker as compared to a baseline pre-treatment level of at least 1% reduction for ALT, AST, TG, TG/HDL-C ratio, Free Fatty acid, AA, MUFA, Palmitoleic acid, Oleic acid, Oleic acid/Stearic acid ratio, Palmitoleic acid/Palmitic acid ratio, Stearic acid/Palmitic acid ratio,

gamma-linolenic acid/Linolenic acid ratio, Adrenic acid/AA ratio, Ferritin, Thioredoxin, TNF-alpha, sTNF-R1, sTNF-R2, Hs-CRP, CTGF, sCD40, Leptin, complement factor D, CK18 fragment, serum HMGB 1, soluble Fas antigen, Hyaluronic acid, Type IV collagen (7s domain), procollagen III peptide or PAI-1; at least 5% increase for EPA or EPA/AA ratio; at least 1% increase for DPA, AA/Homo-gamma-linolenic acid ratio or Serum adiponectin; no worsening of ALP, bilirubin, GGT, Albumin, HDL-C, LDL-C, TC, non-HDL-C, HOMA-IR, HbA1c, Glucose, Fasting plasma glucose, postprandial plasma glucose, OGTT, platelet count or BMI.

[0045] In another embodiment of the invention, the ethyl icosapentate for use in the treatment or alleviation of symptoms of NASH wherein an effective amount of ethyl icosapentate is administered to a subject being possible or definite NASH, and exhibits the described changes of after dosing value in said at least one item selected from the items mentioned in Tables 1 and 2 as compared to a baseline pretreatment level thereof.

[0046] In another embodiment of the invention, the ethyl icosapentate for use in treatment or alleviation of symptoms NASH, wherein the subject is possible or definite NASH and the subject is taking at least one drug selected from the group consisting of lipid-lowering drugs, HMG-CoA reductase inhibitors (stains), fibrates, probucol, ezetimibe, ursodiol (UDCA), taurine, betaine, N-acetylcysteine, s-adenosylmethionine (SAM-e), milk thistle, anti-TNF therapies, probiotics, anti-diabetic medications: biguanides (metformin), insulin, sulfonylureas, alpha-glucosidase inhibitors (acarbose), dipeptidyl-peptidase 4 inhibitors (sitagliptin, saxagliptin, alogliptin, vildagliptin, linagliptin, etc.), phenylalanine derivatives (nateglinide, repaglinide), anti-platelet therapy, anti-thrombotic agents, Glucagon-like peptide-1(GLP-1) receptor agonists (liraglutide, exenatide, taspoglutide, etc.), PDE-4 inhibitor, angiotensin II-1 type receptor antagonist (ARB: losartan, etc.), polyenephosphatidylcholine, antioxidant (vitamine E, vitamin C, nicotinic acid tocopherol,etc.), and pentoxifylline.

[0047] In another embodiment of the invention, the ethyl icosapentate for use in the treatment or alleviation of symptoms of NASH wherein an effective amount of ethyl icosapentate is administered to a subject, wherein the subject is taking at least one drug selected from the group consisting of lipid-lowering drugs, HMG-CoA reductase inhibitors (stains), fibrates, probucol, ezetimibe, ursodiol (UDCA), taurine, betaine, N-acetylcysteine, s-adenosylmethionine (SAM-e), milk thistle, anti-TNF therapies, probiotics, anti-diabetic medications: biguanides (metformin), insulin, sulfonylureas, alpha-glucosidase inhibitors (acarbose), dipeptidyl-peptidase 4 inhibitors (sitagliptin, saxagliptin, alogliptin, vildagliptin, linagliptin, etc.), phenylalanine derivatives (nateglinide, repaglinide), anti-platelet therapy, anti-thrombotic agents, Glucagon-like peptide-1(GLP-1) receptor agonists (liraglutide, exenatide, taspoglutide, etc.), PDE-4 inhibitor, angiotensin II-1 type receptor antagonist (ARB: losartan, etc.), polyenephosphatidylcholine, antioxidant (vitamine E, vitamin C, nicotinic acid tocopherol, etc.), and pentoxifylline.

[0048] In another embodiment of the invention, the ethyl icosapentate for use in the treatment or alleviation of symptoms of NASH wherein an effective amount of ethyl icosapentate is administered to a subject, wherein the subject is taking at least one lipid-lowering drug.

[0049] In another embodiment of the invention, the ethyl icosapentate for use in the treatment or alleviation of symptoms of NASH wherein an effective amount of ethyl icosapentate is administered to a subject, wherein the subject is taking an HMG-CoA reductase inhibitor (statins; pravastatin sodium, simvastatin, pitavastatin calcium, atorvastatin calcium hydrate, rosuvastatin calcium, etc.).

[0050] In another embodiment of the invention, the ethyl icosapentate for use in the treatment or alleviation of symptoms of NASH wherein an effective amount of ethyl icosapentate is administered to a subject, wherein the subject is taking a Glucagon-like peptide-1 (GLP-1) receptor agonist (liraglutide, exenatide, taspoglutide, etc.).

[0051] In another embodiment of the invention, the ethyl icosapentate for use in the treatment or alleviation of symptoms of NASH wherein an effective amount of ethyl icosapentate is administered to a subject in combination with at least one drug selected from the group consisting of lipid-lowering drugs, HMG-CoA reductase inhibitors (stains), fibrates, probucol, ezetimibe, ursodiol (UDCA), taurine, betaine, N-acetylcysteine, s-adenosylmethionine (SAM-e), milk thistle, anti-TNF therapies, probiotics, anti-diabetic medications: biguanides (metformin), insulin, sulfonylureas, alpha-glucosidase inhibitors (acarbose), dipeptidyl-peptidase 4 inhibitors (sitagliptin, saxagliptin, alogliptin, vildagliptin, linagliptin, etc.), phenylalanine derivatives (nateglinide, repaglinide), anti-platelet therapy, anti-thrombotic agents, Glucagon-like peptide-1(GLP-1) receptor agonists (liraglutide, exenatide, taspoglutide, etc.), PDE-4 inhibitor, angiotensin II-1 type receptor antagonist (ARB: losartan, etc.), polyenephosphatidylcholine, antioxidant (vitamine E, vitamin C, nicotinic acid tocopherol, etc.), and pentoxifylline.

[0052] In another embodiment of the invention, the ethyl icosapentate for use in the treatment or alleviation of symptoms of NASH wherein an effective amount of ethyl icosapentate is administered to a subject, wherein the subject is taking an anti-diabetic drug.

[0053] In another embodiment of the invention, the ethyl icosapentate for use in the treatment or alleviation of symptoms of NASH wherein an effective amount of ethyl icosapentate is administered to a subject, wherein the subject is not taking any anti-diabetic drugs.

[0054] In another embodiment of the invention, the ethyl icosapentate for use in the treatment or alleviation of symptoms of NASH wherein an effective amount of ethyl icosapentate is administered to a subject, wherein the subject is not diabetic.

[0055] In another embodiment of the invention, the ethyl icosapentate for use in the treatment or alleviation of symptoms of NASH wherein an effective amount of ethyl icosapentate is administered to a subject, wherein the subject has diabetes.

[0056] In another embodiment of the invention, the ethyl icosapentate for use in the treatment or alleviation of symptoms of NASH wherein an effective amount of ethyl icosapentate is administered to a subject, wherein the subject has impaired glucose tolerance.

[0057] In another embodiment of the invention, the ethyl icosapentate for use in the treatment or alleviation of symptoms of NASH wherein an effective amount of ethyl icosapentate is administered to a subject, wherein the subject has metabolic syndrome.

[0058] In another embodiment of the invention, the ethyl icosapentate for use in reducing at least one marker as compared to a baseline pre-treatment level of Hs-CRP, CTGF, sCD40, Leptin, complement factor D, serum HMGB1, soluble Fas antigen or pro-collagen III peptide in a subject, comprising administering to a subject an effective amount of ethyl icosapentate (EPA-E), wherein the subject has NASH.

[0059] In another embodiment of the invention, the ethyl icosapentate for use in determining efficacy of NASH treatment by (i) administering to a subject an effective amount of EPA-E, (ii) measuring at least one marker of the items mentioned in Tables 1 and 2 during the treatment, (iii) comparing the measured levels of markers to established levels in advance, and optionally (iv) determining whether the treatment is efficacious.

DETAILED DESCRIPTION OF THE INVENTION

[0060] The compositions and methods of the present invention are useful for the treatment of NASH by administration of an effective amount of ethyl icosapentate.

[0061] Icosapentaenoic acid (EPA) is a known omega-3 polyunsaturated, long-chain fatty acid. Omega-3 fatty acids are known as components of oils, such as fish oil, and a variety of commercial products are promoted as containing omega-3 fatty acids, or their esters, derivatives, conjugates and the like. Icosapentaenoic acid (EPA) is also per se known in its ethyl ester form, ethyl icosapentate (EPA-E). According to the present invention, EPA-E can be administered in a composition. EPA-E content in the total fatty acid of the compositions of the present invention are not particularly limited as long as the composition contains EPA-E as its effective component and intended effects of the present invention are attained, high purity EPA-E is preferably used; for example, the composition having a proportion of the EPA-E of preferably 40% by weight or more, more preferably 90% by weight or more, and still more preferably 96.5% by weight or more in total of the fatty acids and their derivatives. EPA-E can be administered to patients in a highly purified form, including the product known as Epadel (Trade mark) (Mochida Pharmaceutical Co., Ltd., Tokyo Japan). The compositions of EPA-E are administered according to the invention to a subject or patient to provide the patient with a dosage of about 0.3-10 g per day of EPA-E, alternatively 0.6-6 g per day, alternatively 0.9-3.6 g per day or specifically about 300 -4000 mg per day or preferably 900-3600 mg per day or more preferably about 1800-2700 mg per day of EPA-E. The compositions of EPA-E are administered according to the invention to a subject or patient preferably one two, or three times per day.

[0062] Since EPAs are highly unsaturated, the preparation as described above preferably contains an antioxidant at an amount effective for suppressing oxidation of the EPAs. Exemplary antioxidants include butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, gallic acid, pharmaceutically acceptable quinone, and alpha-tocopherol.

[0063] The composition to be administered can contain other fatty acids, especially any omega-3 unsaturated fatty acid, especially DHA-E. The ratio of EPA-E/DHA-E in the composition, the content of EPA-E and DHA-E in the total fatty acids and administration amount of EPA-E and DHA-E are not limited but the ratio is preferably 0.8 or more, more preferably 1.0 or more, still more preferably 1.2 or more. The composition is preferably highly purified; for example, the proportion of EPA-E+DHA-E in the fatty acids and their

derivatives is preferably 40% by weight or more, more preferably 80% by weight or more, and still more preferably 90% or more. The daily amount in terms of EPA-E+DHA-E is typically 0.3 to 10.0 g/day, preferably 0.5 to 6.0 g/day, and still more preferably 1.0 to 4.0 g/day. The low content of other long chain saturated fatty acids is preferred, and among the long chain unsaturated fatty acids, the content of omega-6 fatty acids, and in particular, the content of arachidonic acid is preferably as low as less than 2% by weight, and more preferably less than 1% by weight. For example, soft capsule (Lovaza) (Trade mark) or Omacor (Trade mark) containing about 46% by weight of EPA-E and about 38% by weight of DHA-E is commercially available in the U.S., EP and other countries as a therapeutic agent for hyerptriglyceridemia.

[0064] Patients treated for NASH can be administered EPA-E according to the invention for 3, 6 or 9 months, or for 1 year or more and can be administered EPA-E in one, two or three dosage per day, or other multiple doses per day including 1 to about 10, 1 to 8, 1 to 6, 1 to 4 or 1 to 2 dosage units per day as appropriate for patient therapy. The term "dose unit" and "dosage unit" herein refer to a portion of a pharmaceutical composition that contains an amount of EPA-E for a single administration to a subject.

[0065] While meal affects absorption of the EPA-E, and the administration of the EPA-E is preferably conducted during the meal or after the meal, and more preferably immediately after the meal (within 30 minutes after the meal).The self-emulsifying composition has excellent absorption under fasting, and therefore, it exhibits the intended effects even when administered at a timing other than during, after, or immediately after the meal.

[0066] Compositions comprising EPA-E useful for the invention include commercially available compositions of EPA-E, such as Epadel (Trade mark) noted above. Compositions comprising EPA-E may be administered in tablet, capsule, microcapsule, jelly, enteric preparation, extended release preparation, powder or any other solid oral dosage form, as a liquid, emulsion, self-emulsifying composition, as a soft gel capsule or other capsule form, or other appropriate and convenient dosage forms for administration to a patient in need thereof. Compositions can also include pharmaceutically acceptable excipients known to those of ordinary skill in the art including surfactants, oils, co-solvents or combinations of such excipients, together with stabilizers, emulsifiers, preservatives, solubilizers and/or other non-active pharmaceutical ingredients known to those of skill in the art relative to the preparation of pharmaceutical compositions.

[0067] 1. Evaluation Criteria for Patients

[0068] As noted above, the "gold-standard" for a complete diagnosis of NASH involves a liver biopsy. Patients or subjects treated for NASH according to the present invention can also be evaluated for the following criteria, including evaluation prior to initiation of treatment in order to provide a baseline level or score for the criteria as well as evaluation after the dosing regimen to evaluate any improvement in the criteria.

[0069] a. NAS Score:

[0070] A non-alcoholic fatty liver disease activity score (NAS) is defined as the unweighted sum of the values for steatosis (ranging from 0-3), lobular inflammation (ranging from 0-3) and ballooning (ranging from 0-2), thereby providing a range of NAS score of from 0 to 8. (See Kleinen et al., Design and Validation of a Histological Scoring System for Nonalcoholic Fatty Liver Disease, Hepatology, Vol. 41, No.

6, 2005, pp. 1313-1321) Patients treated for NASH according to the present invention can show a NAS score prior to treatment of 4 or more than 4, with a minimum score of 1 each for steatosis and lobular inflammation plus either ballooning or at least 1a sinusoidal fibrosis and a finding of possible or definite steatohepatitis. After dosing/treatment, such as for one year, patients can show a composite NAS score of 3 or less than 3, 2 or less than 2, or 1 or less than 1, together with no worsening in fibrosis. Alternatively, patients can show an improvement in NAS by a value of 2 or more than 2 across at least two of the NAS components, together with no worsening in fibrosis. Alternatively, patients can show an improvement in NAS score by 3 or more than 3, 4 or more than 4, 5 or more than 5, 6 or more than 6, 7 or more than 7, or 8 or more than 8.

[0071]   b. Steatosis:

[0072]   Steatosis is broadly understood to describe a process involving the abnormal retention of lipids within the liver, which accumulation inhibits the normal liver functions. Liver biopsy enables analysis and scoring of steatosis in a patient, with scores ranging from 0-3. Patients treated for NASH according to the present invention can have a steatosis score of 1, 2 or 3, such as between about 2 and about 3. After treatment, it is desired for patients to exhibit no worsening of steatosis, alternatively a reduction of at least 1 in the steatosis score, or a reduction of 2 or 3 in the steatosis score. Steatosis is traditionally graded with a score of 1 indicating the presence of fat droplets in less than 33% of hepatocytes, a score of 2 indicating fat droplets observed in 33-66% of hepatocytes, and a score of 3 indicating observation of fat droplets in greater than 66% of hepato sites. (See Kleinen et al., Design and Validation of a Histological Scoring System for Nonalcoholic Fatty Liver Disease, Hepatology, Vol. 41, No. 6, 2005, pp. 1313-1321)

[0073]   c. Lobular Inflammation:

[0074]   Lobular inflammation is also evaluated upon liver biopsy and scored with values of 0-3. (See Kleinen et al., Design and Validation of a Histological Scoring System for Nonalcoholic Fatty Liver Disease, Hepatology, Vol. 41, No. 6, 2005, pp. 1313-1321 Table 1) Patients to be treated for NASH can have lobular inflammation scores of 1, 2 or 3, alternatively ranging between 1 and 2 or 2 and 3. After treatment, patients can have a reduction in lobular inflammation score of at least 1, alternatively a reduction of 2 or 3 in lobular inflammation score, and at least no worsening of the lobular inflammation score.

[0075]   d. Ballooning:

[0076]   Ballooning of hepatocytes is generally scored with values of 0-2, (See Kleinen et al., Design and Validation of a Histological Scoring System for Nonalcoholic Fatty Liver Disease, Hepatology, Vol. 41, No. 6, 2005, pp. 1313-1321 Table 1), and patients treated for NASH according to the present invention can have ballooning scores of 0-2, including specific values of 1 or 2, and alternatively a score ranging from 1 to 2. After treatment, patients can show at least no worsening of the ballooning score, alternatively a reduction of at least one value lower in the ballooning score, and alternatively a reduction of two in the value of the ballooning score.

[0077]   e. Fibrosis Stage

[0078]   Fibrosis is also evaluated upon liver biopsy and scored with values of 0-4, the scores being defined as: 0 represents no fibrosis, 1 represents perisinusoidal or periportal fibrosis, 1a represents mild, zone 3, perisinusoidal fibrosis; 1b represents moderate zone 3, perisinusoidal fibrosis; 1c

represents portal/periportal fibrosis; 2 represents perisinusoidal and portal/periportal fibrosis; 3 represents bridging fibrosis; and 4 represents cirrhosis. (See Kleinen et al., Design and Validation of a Histological Scoring System for Nonalcoholic Fatty Liver Disease, Hepatology, Vol. 41, No. 6, 2005, pp. 1313-1321) Patients treated according to the present invention can have a fibrosis stage score of 0-3, including 0, 1, 1a, 1b, 1c, 2 or 3, and can have a fibrosis stage score of at least 1a. After treatment, patients can have a fibrosis stage score that is at least no worse than the baseline score, and alternatively can have a reduction in the fibrosis stage score of at least one level, alternatively at least two or three levels.

[0079]   2. Additional Criteria/Markers for Evaluation of Patients

[0080]   As noted above, while liver biopsy is considered the "gold-standard" for clinical assessment of NASH, the condition can also be accompanied or associated with abnormal levels of liver enzymes and other biological blood components. Therefore, patients treated for NASH according to the present invention can also be evaluated for baseline scores of the following criteria before treatment, and evaluated after treatment for possible changes in those criteria. The evaluated criteria can comprise one or more of the following criteria set forth in Tables 1 and 2.

[0081]   In the present invention, a biological sample of the patient is collected and used to obtain measurement values. Specific examples of the biological sample include blood, plasma, serum, urine, body fluids, and tissues, but are not limited thereto. The biological sample is preferably blood, plasma or serum. The biological sample is collected from a subject by a known method.

[0082]   In the present invention, a normal value is measured in accordance with a known measuring method if the normal value is known as one of the blood test indices used to detect NASH, or in accordance with a measuring method following a reference document or the like if a common measuring method for the normal value is not established.

[0083]   For instance, the normal values shown in Tables 1 and 2, except BMI, can be each measured with a biological sample of either blood, plasma or serum. Fatty acids in blood may be used to measure fatty acids. Table 3 shows a list of some reference documents which recite the particulars of the measurement method.

[0084]   Unless otherwise specified, the fatty acid amount and the fatty acid composition ratio as used in the present invention may be the amount and the composition ratio of fatty acids in any of the plasma, serum and liver. It is also possible indeed to use the fatty acid amount and the fatty acid composition ratio in a specified fraction, such as LDL or VLDL in the blood. It, however, is desirable to use the amount and the composition ratio of fatty acids in the plasma or the serum because of the simplicity of measurement. Each fatty acid to be employed for the calculation of the fatty acid amount and the fatty acid composition ratio is not particularly limited in unit of amount, that is to say, its amount may be expressed in mole, mole percent, a unit of weight, percent by weight, or the like. The sole unit, and the sole method of calculating fatty acid amount and the fatty acid composition ratios should be used if the evaluation is to be made by the comparison of the fatty acid amount and the fatty acid composition ratio over time. It is particularly desirable to calculate the fatty acid amount and the fatty acid composition ratio from fatty acid amounts expressed in mole percent of the total amount of fatty acids. The weight/volume concentration (e.g.,

micro g/ml), the mole/volume concentration (e.g., mol/L) or the like may also be used for the calculation.

[0085] In this description, the term "plasma fatty acid" refers to a plasma total fatty acid unless otherwise specified. It is also possible to use a plasma free fatty acid for the inventive index for the evaluation of the subject's condition or therapeutic effects. The term "liver fatty acid" refers to a liver total fatty acid unless otherwise specified. A liver free fatty acid may optionally be used.

[0086] The fatty acid composition may be determined by any method practicable by a person of ordinary skill in the art of the present invention, while it is particularly preferable to determine the composition according to a usual manner.

TABLE 1

Item (Typical Normal Values, Units)	Pre-treatment baseline		After dosing (effect) values	
	Typical Range(s)	Observable Ranges or Values	Typical Range(s)	Observable Ranges or Values
ALT (alanine aminotransferase, GPT) (6-41 U/L)	10-300	Lower limit range values of 10, 50, 100, 150, or 200, upper limit range values of 100, 150, 200, 250, or 300, ranges of 10-300, 10-200, 10-150, 10-100, 100-200, 2000-3000	at least 1% lower	1 to about 95% reduction
AST (asparate aminotransferase, GOT) (9-34 U/L)	10-250	Lower limit range values of 10, 50, 100, 150, or 200, upper limit range values of 100, 150, 200, 250, or 300, ranges of 10-300, 10-200, 10-150, 10-100, 100-200, 200-300	at least 1% lower	1 to about 95% reduction
AST/ALT ratio		upper limit range values of 0.5, 0.7, 0.8, 1, 1.2, 2; ranges of 0.5-2, 0.5-1, 1-2		
alkaline phospatase (ALP) (80-260 IU/L)	80-300	ranges of 50-600	no worsening	no worsening, 1 to about 90% reduction, 300 IU/L or less, 250 IU/L or less
Total bilirubin (0.2-1.2 mg/dL)	High compared to average level of normal subject		no worsening	no worsening, 1 to about 90% reduction,
Gamma-Glutamyl Transferase (GGT or γGTP) (males: 5-60 U/L)	High compared to average level of normal subject		no worsening	no worsening, 1 to about 90% reduction, 100 U/L or less, 70 U/L or less
Albumin (3.8-5.2 g/dl)	Low compared to average level of normal subjects		no worsening	no worsening, 1 to about 90% increase, ranges of 3-6 g/dl, 3.5-5.5 g/dl
HDL-C (high density lipoprotein cholesterol) (35-60- mg/dl)	less than 55	less than 60 mg/dl, 55, 50, 45, 40, 35, 30, 25, or 25 mg/dl; ranges of 25-55, 30-40 mg/dl, 40-50 mg/dl, 50-60 mg/dl, at least 60	no worsening, at least 1% increase	no change, 1-90% increase, 40 mg/dl or more

TABLE 1-continued

Item (Typical Normal Values, Units)	Pre-treatment baseline		After dosing (effect) values	
	Typical Range(s)	Observable Ranges or Values	Typical Range(s)	Observable Ranges or Values
LDL-C (low density lipoprotein cholesterol) (50-130 mg/dl)	100-200	at least 70 mg/dl, 100, 120, 130 140 150, 170, 190, or 200 or a range of 70-300, 70-250, 70-200, 100-250, 100-200, 130-200, 140-180, 100-130, 130-160, 160-190	no worsening	no change, 1-90% reduction less than 160 mg/dl, 140, 130, 120, 100, 70 mg/dl
Triglycerides (TG) (fed or fasting, 50-150 mg/dl)	100-1000	at least 80 mg/dl, 100, 150, 180, 200, 300, 500, 700, 1000, 1200, or 1500, or less than 150, or a range of 100-2500, 100-1500, 100-1000, 150-500, 200-500, 150-300, 150-200, 200-500	at least 1% lower	1 to about 90% reduction, 500 mg/dl or less, 300, 200, 150, 100 mg/dl or less
Total Cholesterol (TC) (100-200 mg/dl)	170-300	a range of 130-300 mg/dl, 200-220, 220-240, 240-260, or at least 260, or less than 200 mg/dl	no worsening	no change, 1-90% reduction
TG and HDL-C	High TG and low HDL-C (ex. TG ≥ 150 mg/dl and HDL ≤ 40 mg/dl	TG: at least 150, 200, 500 mg/dl HDL-C; less than 40, 50 mg/dl	no worsening	
TG/HDL-C ratio	at least 3.75	at least 2, 2.5, 3, 3.75, 4, 5, 10, or ranges of 2-3.75, 3.75-10	at least 1% lower	no worsening, at least 1% lower, or 1-90% reduction
Non-HDL-C (mg/dl)	at least 130	at least 100 mg/dl, 130, 150, 160, 170, 190, a range of 100 to 250	no worsening	no worsening, or at least 1% lower, or less than 130 mg/dl, 150, 160, 170, 190
Free fatty acid (μEq/l) (140-850)	at least 400	less than 400, at least 400, 600, 800, 1000	at least 1% lower	no change, or at least 1 to 90% reduction
Eicosapentaenoic low Acid/Arachidonic Acid (EPA/AA) (ex. (mol/%)/(mol/%)	less than 0.5/low compared to average level or normal subjects	less than 1, 0.75, 0.5, 0.1, ranges of 0.01-2	at least 5% increase	5 to about 200% increase, about 2-200-fold increase
Arachidonic Acid (AA) (ex. mol/%)	High compared to average level of normal subjects		at least 1% lower	no change, 1 to about 90% reduction
Eicosapentaenoic Acid (EPA) (ex. mol/%)	low compared to average level of normal subjects		at least 5% increase	5 to about 200% increase, about 2-500-fold increase
Docosapentaenoic Acid (DPA) (ex. mol/%)	low compared to average level of normal subjects		at least 1% increase	1 to about 95% increase

TABLE 1-continued

Item (Typical Normal Values, Units)	Pre-treatment baseline		After dosing (effect) values	
	Typical Range(s)	Observable Ranges or Values	Typical Range(s)	Observable Ranges or Values
Docosahexaenoic Acid (DHA) (ex. mol/%)	low compared to average level of normal subjects			
DPA/AA ratio	low compared to average level of normal subjects			
DPA/AA ratio	low compared to average level of normal subjects			
DHA/DPA ratio	low compared to average level of normal subjects			
Monounsaturated fatty acid (MUFA) (ex. mol/%)	High compared to average level of normal subjects		at least 1% lower	no change, at least 1% lower
Palmitoleic acid (16:1 n7) (ex. mol/%)	High compared to average level of normal subjects		at least 1% lower	no change, at least 1% lower
Oleic acid (18:1 n9) (ex. mol/%)	High compared to average level of normal subjects		at least 1% lower	no change, a least 1% lower
Oleic acid (18:1 n9)/ stearic acid (18:0) ratio	High compared to average level of normal subjects		at least 1% lower	no change, at least 1% lower
Palmitoleic acid (16:1)/ Palmitic acid (16:0) ratio	High compared to average level of normal subjects		at least 1% lower	no change, at least 1% lower
Stearic acid (18:0)/ Palmitic acid (16:0) ratio	High compared to average level or normal subjects		no change, or at least 1% lower	no change, or at least 1% lower
γ-linolenic acid(18:3 n6)/ Linolenic acid (18:2 n6) ratio	High compared to average level subjects		no change, or at least 1% lower	no change, or at least 1% lower
AA/Homo-γ-linolenic acid (20:3 n6) ratio	low compared to average level of normal subjects		no change, or at least 1% increase	no change, or at least 1% increase
Acrenic acid (22:4 n6)/ AA ratio	High compared to average level of normal subjects		no change, or at least 1% lower	no change, or at least 1% lower
Ferritin (ng/mL)		at least 100, 120, 150, 200, 250, 300, 350, 400, or 500	at least 1% lower	at least 1 to about 95% lower
Thioredoxin (ng/mL)		at least 15, 20, 25, 30, 35, 40, 45, or 50	at least 1% lower	at least 1 to about 95% lower

TABLE 1-continued

Item (Typical Normal Values, Units)	Pre-treatment baseline		After dosing (effect) values	
	Typical Range(s)	Observable Ranges or Values	Typical Range(s)	Observable Ranges or Values
TNFα (Tumor necrosis factor-α) (pg/mL) (1.79 or less)	at least 1.5	at least 1, 1.5, 1.6, 1.7, 1.79, 1.8, 1.9, 2.0, 2.2, 2.5, 3, 3.5, 4, 5, 6, 7 or 10	at least 1% lower	at least 1 to about 95% lower
sTNF-R1 (Tumor necrosis factor receptor I, soluble) (pg/mL)		at least 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1500, or 2000	at least 1% lower	at least 1 to about 95% lower
sTNF-R2 (Tumor necrosis factor receptor II, soluble) (pg/mL)		at least 500, 700, 1000, 1200, 1500, 1700, 2000, 2200, 2500, 2700, or 3000	at least 1% ower	at least 1 to about 95% lower
High Sensitivity C-reactive protien (Hs-CRP, mg/dl)	0.2	0.1 or more, 0.2, 0.3, 0.4, 0.5 or more, ranges of 0.1-1, 0.1-0.8, 0.1-0.5, 0.2-0.5	at least 1% lower	at least 5 to about 95% lower
Connective Tissue Growth Factor (CTGF)	High compared to average level of normal subject		at least 1% lower	at least 5 to about 95% lower
Serum Soluble CD40 (sCD40, pg/ml)		5 pg/ml or more, 10, 20, 30, 50, 70, 100, 120, 150, 170, 200, 220, 250, 300, 350, 400, 450, 500 or more	at least 1% lower	at least 5 to about 95% lower
Insulin resistance Index (HOMA-IR) (1.6 or less)	1.5 or more	1.6 or less/1.5 or more, 1.6, 2, 2.5, 3, 3.5, 4	no worsening	no change, at least 1 to about 50% lower
Glycated hemoglobin (HbA1c) (4.3-5.8%)	5.7 or more	a range of 4.3-5.8, 5.7-6.4, 5.8-6.5, 6.5-7.0, 7.0-8.0/5.7 or more, 5.8, 6, 6.5, 7, 7.5, 8, or 8.5	no worsening	no change, at least 1 to about 50% lower
Fasting plasma glucose (FRG) (mg/dl) (less than 100)	100 or more	less than 100/ 100 or more, 110, 120, 126, 130, 150, 200, 250, 300/ ranges of 100-110, 100-126	no worsening	no change, or at least 1 to about 50% lower
Postprandial plasma glucose (after a meal)	140 or more	less than 140, 160, 200/ 140 or more, 170, 180, 200, 250, 300, 350 400/ranges of 140-200, 140-170, 170-200	no worsening	no change, or at least 1 to about 50% lower
two-hour glucose levels on the 75-g oral glucose tolerance test (mg/dl) (OGTT)	140-200	less than 140, 160, 200/140 or more, 170, 180, 200, 250, 300, 350, 400/ ranges of 140-200, 140-170, 170-200	no worsening	no change, or at least 1 to about 50% lower

TABLE 1-continued

Item (Typical Normal Values, Units)	Pre-treatment baseline		After dosing (effect) values	
	Typical Range(s)	Observable Ranges or Values	Typical Range(s)	Observable Ranges or Values
Leptin (ng/ml)		5 ng/ml or more, 10, 12, 15, 17, 20, 22, 25, 30, 35, 40 or more	at least 1% lower	at least 1 to about 95% reduction
Serum adiponectin (μg/mL)		5 μg/mL or less, 4.5, 4, 3.5, or 3 μg/mL or less	at least 1% increase	no change, at least 1 to about 95% increase
complement factor D	High compared to average level of normal subject		at least 15% lower	at least 1 to about 95% reduction
CK18 fragment	High compared to average level of normal subject		at least 1% lower	at least 1 to about 95% reduction
serum High mobility group box 1 protein (HMGB1)	High compared to average level of normal subject		at least 1% lower	at least 1 to about 95% reduction
soluble Fas antigen (CD95, sFas)	High compared to average level of normal subject		at least 1% lower	at least 1 to about 95% reduction
Hyaluronic acid (50 ng/mL or less)		25 ng/mL or more, 50, 70, 100, 120, 150, 200, 250, or 300 or more; 200 mL or less, 100, 70, or 50 or less	at least 1% lower	at least 1 to about 95% reduction
Type IV collagen (7s domain) (6 ng/mL or less)		5 ng/mL or more, 6, 7, 8, 10, 12, 15, or 20 or more; 25 ng/mL or less, 20, 15, 10, or 6 or less	at least 1 % lower	at least 1 to about 95% reduction
procollagen III peptide 0.3-0.8 U/ml		0.2 U/ml or more, 0.3, 0.5, 0.7, 1, 1.2, 1.5, 2, 2.5, 3, 3.5, or 4 or more; 10 or less, 8, 5, 3, 1, or 0.8 or less	at least 1% lower	at least 1 to about 95% reduction
PAI-1 (ng/mL) 50 or less	50 or more			
platelet count 150000-400000/μl	150000-300000	400000/μl or less, 300000, 200000/a range of 150000-300000	no change	no change, at least 1% increase
BMI	18.5-40	18.5 or more, 20, 25, 30, 35, 40, or 50 or more; /50 or less, 40, 30, 25, 20 or 18.5 or less; or range of 18.5-25, 25-30, 30-35. 35-40	no change	no change, at least 1% reduction
Direct Bilirubin (0-0.4 mg/dL)	High compared to average level of normal subject		No worsening	No worsening, 1 to about 90% reduction

TABLE 1-continued

	Pre-treatment baseline		After dosing (effect) values	
Item (Typical Normal Values, Units)	Typical Range(s)	Observable Ranges or Values	Typical Range(s)	Observable Ranges or Values
Oleic acid (C18:1 n9)/ Palmitic acid (C16:0)ratio	High compared to average level of normal subject		At least 1% lower	No change, at least 1% lower
EPA/AA ratio and Hs-CRP	Low EPA/AA ratio and high Hs-CRP	EPA/AA ratio being 1.0 or less, 0.75, 0.6, 0.5, 0.4, 0.25 or less; Hs-CRP being 0.1 mg/dl or higher, 0.2 mg/dl or higher, 0.3 mg/dl or higher		EPA/AA ratio increases; Hs-CRP decreases
Interleukin-1 receptor antagonist (IL-1 ra)	High compared to average level of normal subject		at least 1% lower	at least 1 to about 95% lower
sPLA2(Secretory phospholipase A2) group II A: type2A, type II A	High compared to average level of normal subject		at least 1% lower	at least 1 to about 95% lower
sPLA2 activity	Low compared to average level of normal subjects	No worsening		
Interleukin 2(IL-2)	High compared to average level of normal subject		at least 1% lower	at least 1 to about 95% lower
ApolipoproteinA-IV	High compared to average level of normal subject		at least 1% lower	at least 1 to about 95% lower
ApolipoproteinC-II	High compared to average level of normal subject		at least 1% lower	at least 1 to about 95% lower
CCL2: Chemokine(C-C motif) ligand 2	High compared to average level of normal subject		at least 1% lower	at least 1 to about 95% lower
Thrombospondin 1: TSP1	High compared to average level of normal subject		at least 1% lower	at least 1 to about 95% lower
IL-3 receptor (interleukin-3 receptor) alpha chain	High compared to average level of normal subject		at least 1% lower	at least 1 to about 95% lower
Lymphocyte antigen 6 comlex, locus D	High compared to average level of normal subject		at least 1% lower	at least 1 to about 95% lower
MMP12: Matrix metallopeptidase 12	High compared to average level of normal subject		at least 1% lower	at least 1 to about 95% lower
MMP13: Matrix metallopeptidase 13	High compared to average level of normal subject		at least 1% lower	at least 1 to about 95% lower
Trehalase (brush-border membrane glycoprotein)	High compared to average level of normal subject		at least 1% lower	at least 1 to about 95% lower

TABLE 1-continued

Item (Typical Normal Values, Units)	Pre-treatment baseline		After dosing (effect) values	
	Typical Range(s)	Observable Ranges or Values	Typical Range(s)	Observable Ranges or Values
TIMP1: Tissue inhibitor of metalloproteinase 1	High compared to average level of normal subject		at least 1% lower	at least 1 to about 95% lower
COL1a1: Procollagen type I, alpha 1	High compared to average level of normal subject		at least 1% lower	at least 1 to about 95% lower
Complement factor D (adipsin)	High compared to average level of normal subject		at least 1% lower	at least 1 to about 95% lower
TNFR (tumor necrosis factor receptor) superfamily, member 19 (TAJ)	High compared to average level of normal subject		at least 1% lower	at least 1 to about 95% lower
TNFAIP (tumor necrosis factor alpha induced protein) 6	High compared to average level of normal subject		at least 1% lower	at least 1 to about 95% lower
VLDLR (Very low density lipoprotein receptor)	High compared to average level of normal subject		at least 1% lower	at least 1 to about 95% lower
Lipoprotein lipase	High compared to average level of normal subject		at least 1% lower	at least 1 to about 95% lower
Ear (Eosinophil associated ribonuclease) A family, members 1, 2, 3, and 12	High compared to average level of normal subject		at least 1% lower	at least 1 to about 95% lower
INSL5: Insulin like 5	Low compared to average level of normal subjects		At least 1% increase	
TGF β 2: Transforming growth factor beta 2	Low compared to average level of normal subjects		At least 1% increase	
HAMP: Hepcidin antimicrobial peptide 1	Low compared to average level of normal subjects		At least 1% increase	
Lipase member H: LIPH	Low compared to average level of normal subjects		At least 1% increase	
CYP7B1: Cytochrome P450 family 7 subfamily b polypeptide 1	Low compared to average level of normal subjects		At least 1% increase	

TABLE 2

Item Typical Normal Values, Units)	Pre-treatment baseline		After dosing (effect) values	
	Typical Range(s)	Observable Ranges or Values	Typical Range(s)	Observable Ranges or Values
1 1-HETE (11-hydroxy-5,8,12,14-eicosatetraenoic acid)	High compared to average level of normal subject		at least 1% lower	at least 1 to about 95% lower
Total HEPEs (hydroxy-eicosapentaenoic acids)/total HETEs (Hydroxy-eicosatetraenoic Acids) ratio	Low compared to average level of normal subjects		At least 1% increase	
Glycocholate	High compared to average level of normal subject	Twice or more than twice as high as normal subject	at least 1% lower	
Taurocholate	High compared to average level of normal subject	Twice or more than twice as high as normal subject	at least 1% lower	
Glycocholate/ Glycine ratio	High compared to average level of normal subject	Twice or more than twice as high as normal subject	at least 1% lower	
Taurocholate/ Taurine ratio	High compared to average level of normal subject	Twice or more than twice as high as normal subject	at least 1% lower	
Total fatty acids of 20 to 24 carbon atoms (C20-24)/total fatty acids of 16 carbon atoms (C16) ratio (ex. μg/ml/μg/ml, wt %/wt %)	Low compared to average level of normal subjects		At least 1% increase	
Total omega-3 polyunsaturated fatty acids of 20 to 24 carbon atoms(C20-24)/ total fatty acids of 16 carbon atoms (C16) ratio (ex. μg/ml/μg/ml, wt %/wt %)	Low compared to average level of normal subjects		At least 1% increase	
Total fatty acids of 20 to 24 carbon atoms(C20-24)/ total fatty adds of 18 carbon atoms (C18) ratio (ex. μg/ml/μg/ml, wt %/wt %)	Low compared to average level of normal subjects		At least 1% increase	
Total omega-3 polyunsaturated fatty acids of 20 to 24 carbon atoms(C20-24)/ total weight of fatty acids of 18 carbon atoms (C18) ratio (ex. μg/ml/μg/ml, wt %/wt %)	Low compared to average level of normal subjects		At least 1% increase	

TABLE 2-continued

Item Typical Normal Values, Units)	Pre-treatment baseline		After dosing (effect) values	
	Typical Range(s)	Observable Ranges or Values	Typical Range(s)	Observable Ranges or Values
IL-10 (Interleukin-10)	No change or Low compared to average level of normal subjects		At least 1% increase	
Small dense LDL	No change or High compared to average level of normal subjects	at least 20 mg/dl, 25, 30, 40, 50, at least 60 mg/dl	at least 1% lower	
RLP-TG (Remnant-like lipoprotein particles-triglyceride)	No change or High compared to average level of normal subjects	at least 10 mg/dl, 20, 30, 40, 50, 70, 80, 100, 120, at least 150 mg/dl	at least 1% lower	
RLP-C (Remnant-like lipoprotein particles-cholesterol)	No change or High compared to average level of normal subjects	At least 4.5 mg/dl, 5, 5.2, 5.5, 6, 8, 10, 12, at least 15 mg/dl	at least 1% lower, or no change	
Whole Blood viscosity (cP/mPa • s)		High compared to average level of normal subject	at least 1% lower	at least 1% lower
Plasma viscosity (cP/mPa • s)		High compared to average level of normal subject	No worsening	
IL-10 (Interleukin-10)/ TNFα ratio	Low compared to average level of normal subject		At least 1% increase	
IL-10 (Interleukin-10)/ sCD40 ratio	Low compared to average level of normal subject		At least 1% increase	
Serum adiponectin/ TNFα ratio	Low compared to average level of normal subject		At least 1% increase	
Serum adiponectin/ sCD40 ratio	Low compared to average level of normal subject		At least 1% increase	

TABLE 3

11-HETE	Prostaglandins Other Lipid Mediat. 2011 April; 94(3-4): 81-7.
HETE, HEPE	Analysis of omega-3 and omega-6 fatty acid-derived lipid metabolite formation in human and mouse blood samples.
Glycocholate	Metabolism. 2011 March; 60(3): 404-13.
Taurocholate	Plasma metabolomic profile in nonalcoholic fatty liver disease.
IL-10	Obes Surg. 2010 July; 20(7): 906-12. Pro- and anti-inflammatory cytokines in steatosis and steatohepatitis.
Small dense LDL	Diabetol Metab Syndr. 2012 July 18; 4(1): 34. Fatty liver in men is associated with high serum levels of small, dense low-density lipoprotein cholesterol.
RLP-TG	Clinica Chimica Acta 413 (2012) 1077-1086
RLP-C	The characteristics of remnant lipoproteins in the fasting and postprandial plasma.
Connective Tissue Growth Factor (CTGF)	Regul Pept. 2012 September 4; 179(1-3): 10-14. Connective tissue growth factor level is increased in patients with liver cirrhosis but is not associated with complications or extent of liver injury.
Serum Soluble CD40 (sCD40)	Apoptosis 2004; 9: 205-210 Role of circulating soluble CD40 as an apoptotic marker in liver disease.
Complement factor D	Int Immunopharmacol. 2009 November; 9(12): 1460-3. Serum adipsin levels in patients with seasonal allergic rhinitis: preliminary data.

TABLE 3-continued

CK18 fragment	Aliment Pharmacol Ther. 2010 December; 32(11-12): 1315-22. A new composite model including metabolic syndrome, alanine aminotransferase and cytokeratin-18 for the diagnosis of non-alcoholic steatohepatitis in morbidly obese patients.
Serum High mobility group box 1 protein (HMGB1)	PLoS One. 2012; 7(4): e34318. Diagnostic significance of serum HMGB1 in colorectal carcinomas.
fatty acid amount and fatty acid composition ratio in blood	Clinical Nutrition (2002) 21 (3) 219-223 Plasma total and free fatty acids composition in human non-alcoholic steatohepatitis.
Ferritin, Thioredoxin	J Hepatol. 2003 January; 38(1): 32-8. Serum thioredoxin levels as a predictor of steatohepatitis in patients with nonalcoholic fatty liver disease.
sTNF-R1, sTNF-R2	Diabetes Care. 2010 October; 33(10): 2244-9. Epub 2010 July 27. Association between systemic inflammation and incident diabetes in HIV-infected patients after initiation of antiretroviral therapy.
Hs-CRP	J Hepatol. 2011 September; 55(3): 660-5. C-reactive protein levels in relation to various features of non-alcoholic fatty liver disease among obese patients.
soluble Fas antigen (CD95, sFas)	J Transl Med. 2009 July 29; 7: 67. Short term effects of milrinone on biomarkers of necrosis, apoptosis, and inflammation in patients with severe heart failure.
Whole Blood viscosity	British Journal of Haematology, 1997 96, 168-173
Plasma viscosity	Blood viscosity and risk of cardiovascular events: the Edinburgh Artery Study
Items in Table1(1-8, 1-9, 1-10)	WO2011/046204

Example—Treatment of NASH

[0087] To evidence the usefulness of the present invention for the treatment of NASH, patients are evaluated for inclusion in the treatment regimen, treated for NASH, and evaluated for effectiveness of the treatment as follows:

[0088] Patients are histologically diagnosed with NASH within six months of the initiation of treatment and are willing to submit to a further liver biopsy at the end of the treatment regimen to evaluate effectiveness of the treatment.

[0089] 1. Inclusion Criteria:

[0090] Patients are definitively diagnosed with NASH (via liver biopsy) and exhibit a NAS score of greater than or equal to 4 by a pathologist.

[0091] Patients can be of either gender but are greater than 18 years of age.

[0092] Patients with diabetes, impaired glucose tolerance or metabolic syndrome that have been on stable dosage of anti-diabetic agents for at least six months prior to the liver biopsy are suitable for treatment.

[0093] 2. Exclusion Criteria:

[0094] Patients may be excluded for treatment based upon an inability or unwillingness to have a liver biopsy for confirming the diagnosis of NASH, having a diagnosis of cirrhosis by pathologist, exhibiting previous bariatric surgery or biliary diversion (i.e. gastric bypass), esophageal banding or gastric banding; serum ALT values of greater than 330 UL, drug use associated with steatohepatitis within 6 months prior to initiation of treatment, such as with corticosteroids, high dose estrogens, methodtrexate, amiodarone, anti-HIV drugs, tamoxifen, or diltiazem; alcohol consumption of greater than 30 g/day, concurrently or for more than three consecutive months within five years prior treatment; a blood alcohol level greater than 0.02% at the time of baseline evaluation; evidence of active substance abuse; including prescription or recreational drugs, the presence of other liver diseases such as acute or chronic hepatitis C, acute or chronic active hepatitis B, Wilson's, autoimmune, alpha-1-antitrypsin and hemo-

chromatosis or HIV infection; renal insufficiency; symptomatic coronary; peripheral or neurovascular disease; symptomatic heart failure or advanced respiratory disease requiring oxygen therapy; a history of cerebral or retinal hemorrhage or other bleeding diathesis.

[0095] 3. Key Criteria for Measuring Baseline and Post Treatment Values:

[0096] Patients to be treated are evaluated for one or more of the following criteria.

[0097] a) Primary Long-Term Efficacy Outcome Measure

[0098] Histology at treatment month 12.5 to evaluate the NAS score, as a comparison to the baseline score measured pre-treatment. (NAS)

[0099] b) Primary Short-Term Efficacy Outcome Measure

[0100] Change from baseline in ALT levels at Month 3 and Month 6 of treatment.

[0101] c) Secondary Efficacy Outcome Measures

[0102] Overall NAS score

[0103] Feature scores including fibrosis, ballooning degeneration, inflammation and steatosis

[0104] Liver function tests (AST, alkaline phosphataise, bilirubin, GGT, Albumin) Cholesterol (including HDL and LDL)

[0105] Triglycerides

[0106] Fatty acid assay

[0107] Ferritin

[0108] Thioredoxin

[0109] Pro-inflammatory cytokines (TNF-alpha, sTNF-R1, sTNF-R2, Hs-CRP, CTGF, sCD40)

[0110] Insulin sensitivity (HOMA-IR)

[0111] HbA1c

[0112] Glucose

[0113] Leptin, Serum adiponectin and complement factor D

[0114] CK18 fragment and Serum HMGB1

[0115] soluble Fas antigen

[0116] Hyaluronic acid

[0117] Type IV collagen (7S domain)

[0118] Procollagen III peptide

[0119] d) Safety Outcome Measures

[0120] Adverse Events

[0121] Hematology/biochemistry/urinalysis

[0122] ECG (including QT/QTc measurement)

[0123] e) Pharmacokinetic Outcome Measures

[0124] EPA, DPA and DHA

[0125] Day 1

[0126] On Day 1, samples for plasma concentration are obtained at predose and 0.5, 1, 2, 4, 5 and 6 hours after Dose #1 and Dose #3; after Dose #2, samples are obtained at 2, 4, 5 and 6 hours post-dose. After Dose #3, samples are also obtained at 8 and 12 hours post-dose (20 and 24 hours after Dose #1 [prior to the morning dose on Day 2]) C_{max} (Dose #1 and Dose #2s) and C_{max}, T_{max}, $T_{1/2}$, AUG_{0-t} after third Dose are derived from plasma concentrations

[0127] Days 29, 85, 169 and 365 (Visits 3, 5, 7 and 9)

[0128] A single sample is obtained prior to the morning dose (trough) on Visits 3, 5, 7 and 9. Css is determined from plasma concentrations

[0129] 4. Concomitant and Medications:

[0130] Particular medications can be prohibited or permitted during treatment according to the invention for NASH.

[0131] The following medications can be prohibited during treatment:

[0132] Omega-3-acid ethyl esters and omega-3-PUFA containing supplements>200 mg per day

[0133] Vitamin E>60 IU per day

[0134] Thiazolidinediones (e.g. pioglitazone, rosiglitazone)

[0135] The following medications may be used during the treatment according to the specified restrictions:

[0136] Subjects may continue prescription or over-the-counter medications or herbal remedies such as HMG-CoA reductase inhibitors (stains), fibrates, probucol, ezetimibe, ursodiol (UDCA), taurine, betaine, N-acetylcysteine, s-adenosylmethionine (SAM-e), milk thistle, anti-TNF therapies, or probiotics

[0137] Subjects may continue the following anti-diabetic medications: biguanides (metformin), insulin, sulfonylureas, alpha-glucosidase inhibitors (acarbose), dipeptidyl-peptidase 4 inhibitors (sitagliptin, saxagliptin), and phenylalanine derivatives (nateglinide, repaglinide)

[0138] Subjects may continue receiving anti-platelet therapy and anti-thrombotic agents (e.g. warfarin, Aspirin (ASA), and clopidogrel) after study commencement should be monitored closely during the study for bleeding problems.

[0139] 5. Treatment

[0140] Patients are treated with EPA-E comprised of two daily treatments, but the total daily dose of EPA-E being 1800 mg or 2700 mg per day, divided into dosage amounts of 600 mg TID or 900 mg TID, respectively.

[0141] Treatment with EPA-E is continued for 12 months.

[0142] Patients are periodically evaluated for the selected criteria, such as at month 1, month 3, month 6 and month 12 of treatment.

[0143] After 12 months of treatment, patients are evaluated for the criteria noted above, including liver biopsy, NAS score, steatosis, lobular inflammation, ballooning and fibrosis stage, and one or more of the other criteria listed above in Tables 1 and 2.

[0144] The invention being thus described, it will be apparent to one of ordinary skill in the art that various modifications of the materials and methods for practicing the invention can be made. Such modifications are to be considered within the scope of the invention as defined by the following claims.

[0145] Each of the references from the patent and periodical literature cited herein is hereby expressly incorporated in its entirety by such citation.

1. Ethyl icosapentate for use in the treatment or alleviation of symptoms of non-alcoholic steatohepatitis (hereinafter abbreviated as NASH) in a subject in need thereof, wherein:
  (a) a baseline level in a subject having NASH of at least one criteria selected from the group consisting of NAS score, steatosis score, lobular inflammation score, ballooning score and fibrosis stage is determined; and
  (b) an effective amount of ethyl icosapentate (EPA-E) is administered to said subject.

2. The ethyl icosapentate for use according to claim 1, wherein said subject has a NAS score of 4 or more than 4.

3. The ethyl icosapentate for use according to claim 1 or 2, wherein said subject is characterized by at least one criteria selected from the group consisting of a baseline ALT value of 10 to 300 U/L; a baseline AST value of 10 to 250 U/L; a baseline steatosis grade of 2 to 3; and a baseline lobular inflammation grade of 2 to 3.

4. The ethyl icosapentate for use according to any one of claims 1 to 3, wherein after said administration of said EPA-E for about one year, said subject exhibits at least one improvement selected from the group consisting of a reduced ALT value as compared to said baseline ALT value; a reduced AST value as compared to said baseline AST value; a reduced steatosis grade as compared to said baseline steatosis grade; and a reduced lobular inflammation grade as compared to said baseline lobular inflammation grade.

5. The ethyl icosapentate for use according to any one of claims 1 to 4, wherein said ethyl icosapentate is administered to said subject in an amount of 300 to 4000 mg per day.

6. The ethyl icosapentate for use according to any one of claims 1 to 5, wherein said subject is further characterized by having at least one condition selected from the group consisting of high TG and low HDL-C, diabetes, impaired glucose tolerance and metabolic syndrome.

7. The ethyl icosapentate for use according to any one of claims 4 to 6, wherein said reduced ALT value is at least 5% lower than said baseline ALT value and/or said reduced AST value is at least 5% lower than said baseline AST value.

8. The ethyl icosapentate for use according to any one of claims 1 to 7, further comprising determining in said subject prior to treatment a baseline level in serum of at least one member selected from the group consisting of ALT in a range of 10 to 300 U/L, AST in a range of 10 to 250 U/L, HDL-C in a range of 25 to 55 mg/dl, LDL-C in a range of 100 to 200 mg/dl, triglycerides in a range of 100 to 1000 mg/dl, TC in a range of 170 to 300 mg/dl, High TG and low HDL-C, TG/HDL-C ratio in a range of 3.75 to 10, non-HDL-C in a range of 100 to 250 mg/dl, Free fatty acid in a range of 400 to 1000 micro Eq/L, HOMA-IR in a range of 1.5 to 5, HbA1c in a range of 5.7 to 10%, Fasting plasma glucose in a range of 100 to 200 mg/dl.

9. The ethyl icosapentate for use according to any one of claims 1 to 8, wherein after administration of ethyl icosapentate for at least 3 months, said subject exhibits the following changes in said at least one marker as compared to the baseline level of at least 1% reduction for ALT, AST, TG, TG/HDL ratio, Free fatty acid, AA, MUFA, Palmitoleic acid, Oleic acid, Oleic acid/Stearic acid ratio, Palmitoleic acid/Palmitic acid ratio, Adrenic acid/AA ratio, Ferritin, Thioredoxin,

TNF-alpha, sTNF-R1, sTNF-R2, Hs-CRP, CRGF, sCD40, Leptin, complement factor D, CK18 fragment, serum HMGB1, soluble Fas antigen, Hyaluronic acid, Type IV collagen (7s domain), procollagen III peptide or PAI-1; at least 5% increase for EPA or EPA/AA ratio; at least 1% increase for DPA, AA/Homo-gamma-linolenic acid ratio or Serum adiponectin; no worsening of ALP, bilirubin, GGT, Albumin, HDL-C, LDL-C, TC, non-HDL-C, HOMA-IR, HbA1c, Glucose, Fasting plasma glucose, postprandial plasma glucose, OGTT, platelet count or BMI.

10. The ethyl icosapentate for use according to any one of claims 1 to 9, wherein: the NAS score in said subject after administering (i) to a composite score of 3 or less than 3 and no worsening of said fibrosis stage score, or (ii) by 2 or more than 2 across at least two of the NAS components and no worsening of said fibrosis stage score is improved.

11. Ethyl icosapentate for use in the treatment or alleviation of symptoms of NASH in a subject in need thereof, wherein:

(a) a baseline level in said subject having NASH of at least one criteria selected from the group consisting of NAS score, steatosis score, lobular inflammation score, ballooning score and fibrosis stage is determined;

(b) an effective amount of ethyl icosapentate (EPA-E) is administered to said subject; and

(c) the NAS score in said subject (i) to a composite score of 3 or less than 3 and no worsening of said fibrosis stage score, or (ii) by 2 or more than 2 across at least two of the NAS components and no worsening of said fibrosis stage score is improved.

12. The ethyl icosapentate for use according to claim 11, wherein said subject has a baseline NAS score of 4 or more than 4.

13. The ethyl icosapentate for use according to claim 11 or 12, wherein after said administration of said EPA-E once daily for about one year, said subject exhibits at least one improvement selected from the group consisting of a reduced ALT value as compared to said baseline ALT value; a reduced AST value as compared to said baseline AST value; and a reduced lobular inflammation grade as compared to said baseline lobular inflammation grade.

14. The ethyl icosapentate for use according to claim 13, wherein said reduced ALT value is at least 10% lower than said baseline ALT value and/or said reduced AST value is at least 10% lower than said baseline AST value.

15. The ethyl icosapentate for use according to any one of claims 11 to 14, wherein after administration of ethyl icosapentate for at least 12 months, said subject exhibits at least 10% reduction as compared to the baseline level of at least one marker selected from the group consisting of ALT, AST, TG, Ferritin, Thioredoxin, TNF-alpha, hyaluronic acid and Type IV collagen (7S domain); at least 5% reduction for HDL, LDL, EPA/AA, AA, DPA, STNF-R1, STNF-R2, HSCRP, CTGF, SCD40, Leptin, Seum adiponectin, complement factor D, CK18 fragment, serum HMGB 1, soluble Fas antigen or procollegen III peptide and no worsening of HOMA-IR, HbA1c, glucose, platelet count or BMI.

16. Ethyl icosapentate for use in the treatment or alleviation of symptoms of NASH in a subject in need thereof, wherein:

(a) a subject having NASH characterized by baseline levels in said subject of ALT of between 5 to 300 and at least one criteria selected from the group consisting of NAS score of 4 or more than 4, steatosis score of 1 or more

than 1, lobular inflammation score of 1 or more than 1, and either (i) fibrosis stage of at least 1a or ballooning is identified;

(b) an effective amount of ethyl icosapentate (EPA-E) is administered to said subject; and

(c) the NAS score in said subject (i) to a composite score of 3 or less than 3 and no worsening of said fibrosis stage score, and (ii) by 2 or more than 2 across at least two of the NAS components and no worsening of said fibrosis stage score is improved.

17. The ethyl icosapentate for use according to any one of claims 1 to 16, wherein said ethyl icosapentate is administered to said subject in an amount of 300 to 4000 mg per day.

18. The ethyl icosapentate for use according to any one of claims 11 to 17, wherein after administration of ethyl icosapentate for at least 12 months, said subject exhibits at least 10% reduction as compared to the baseline level of at least one member of the group consisting of ALT, AST, TG, Ferritin, Thioredoxin, TNF-alpha, hyaluronic acid or Type IV collagen (7S domain), at least 5% reduction for HDL, LDL, EPA/AA, AA, DPA, STNF-R1, STNF-R2, HSCRP, CTGF, SCD40, Leptin, Seum adiponectin, complement factor D, CK18 fragment, serum HMGB1, soluble Fas antigen or procollegen III peptide and no worsening of HOMA-IR, HbA1c, glucose, platelet count or BMI.

19. The ethyl icosapentate for use according to any one of claims 11 to 18, wherein said EPA-E is administered twice daily in dosage amounts of 600 mg or 900 mg.

20. Ethyl icosapentate for use in the treatment or alleviation of symptoms of NASH in need thereof, wherein:

(a) an effective amount of ethyl icosapentate (EPA-E) is administered to a subject, wherein said subject has NASH and is characterized by baseline levels in said subject of ALT of between 5 to 300 and at least one criteria selected from the group consisting of NAS score of 4 or more than 4, steatosis score of 1 or more than 1, lobular inflammation score of 1 or more than 1 and either (i) fibrosis stage of at least 1a or (ii) ballooning; and

(c) the NAS score in said subject (i) to a composite score of 3 or less than 3 and (ii) by 2 or more than 2 across at least two of the NAS components, and no worsening of said fibrosis stage score is improved after administration.

21. The ethyl icosapentate for use according to claim 20, wherein after administration of ethyl icosapentate for at least 12 months, said subject exhibits at least 10% reduction as compared to the baseline level for at least one member selected from the group consisting of ALT, AST, TG, Ferritin, Thioredoxin, TNF-alpha, hyaluronic acid or Type IV collagen (7S domain); at least 5% reduction for HDL, LDL, EPA/AA, AA, DPA, STNF-R1, STNF-R2, HSCRP, CTGF, SCD40, Leptin, Seum adiponectin, complement factor D, CK18 fragment, serum HMGB 1, soluble Fas antigen or procollegen III peptide and no worsening of HOMA-IR, HbA1c, glucose, platelet count or BMI.

22. Ethyl icosapentate for use a reducing steatosis, liver lobular inflammation and/or liver fibrosis in a subject in need thereof, wherein:

(b) an effective amount of ethyl icosapentate (EPA-E) is administered to a subject;

(c) the steatosis and lobular inflammation condition of said subject, and no worsening of said fibrosis stage score is improved after administration; and

(d) said subject exhibits the following changes in said at least one marker as compared to a baseline pretreatment

level of at least 1% reduction for ALT, AST, TG, TG/HDL ratio, Free fatty acid, AA, MUFA, Palmitoleic acid, Oleic acid, Oleic acid/Stearic acid ratio, Palmitoleic acid/Palmitic acid ratio, Stearic acid/Palmitic acid ratio, gamma-linolenic acid/Linolenic acid ratio, Adrenic acid/AA ratio, Ferritin, Thioredoxin, TNF-alpha, sTNF-R1, sTNF-R2, Hs-CRP, CTGF, sCD40, Leptin, complement factor D, CK18 fragment, serum HMGB1, soluble Fas antigen, Hyaluronic acid, Type IV collagen (7s domain), procollagen III peptide or PAI-1; at least 5% increase for EPA or EPA/AA ratio; at least 1% increase for DPA, AA/Homo-gamma-linolenic acid ratio or Serum adiponectin; no worsening of ALP, bilirubin, GGT, Albumin, HDL-C, LDL-C, TC, non-HDL-C, HOMA-IR, HbA1c, Glucose, Fasting plasma glucose, postprandial plasma glucose, OGTT, platelet count or BMI.

23. The ethyl icosapentate for use according to claim **22**, wherein said ethyl icosapentate is administered to said subject in an amount of 300 or 4000 mg per day.

24. Ethyl icosapentate for use in the treatment or alleviation of symptoms of NASH in a subject in need thereof, wherein an effective amount of EPA-E is administered to a subject, wherein the subject is possible or definite NASH, and is characterized by the baseline pretreatment level in the subject of at least one criteria selected from the group consisting of ALT in a range of 10 to 300 U/L, AST in a range of 10 to 250 U/L, HDL/C in a range of 25 to 55 mg/dl, LDL-C in a range of 100 to 200 mg/dl, triglycerides in a range of 100 to 1000 mg/dl, TC in a range of 170 to 300 mg/dl, High TG and low HDL-C, TG/HDL-C ratio in a range of 3.75 to 10, non-HDL-C in a range of 100 to 250 mg/dl, Free fatty acid in a range of 400 to 1000 micro Eq/L, HOMA-IR in a range of 1.5 to 5, HbA1c in a range of 5.7 to 10%, Fasting plasma glucose in a range of 100 to 200 mg/dl, impaired glucose tolerance and metabolic syndrome.

25. Ethyl icosapentate for use in the treatment or alleviation of symptoms of NASH in a subject suspected of having NASH, wherein an effective amount of EPA-E is administered to a subject, wherein the subject is possible or definite NASH, and is characterized by the baseline pretreatment level in the subject of at least one criteria selected from the group consisting of low level of EPA, DPA, DHA, EPA/AA, DHA/AA. DHA/DPA, AA/Homo-gamma-linolenic acid: and high level of AA, MUFA, Palmitoleic acid, Oleic acid, Oleic acid/Stearic acid, Palmitoleic acid/Palmitic acid, gamma-linolenic acid/Linolenic acid, Adrenic acid/AA compared to each average level in subjects with NASH.

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