

**MIRICORILANT TREATMENT FOR FATTY LIVER DISEASES and its EFFECTS on
LIVER FAT CONTENT, FATTY ACIDS, ACYLGLYCEROLS, and SECONDARY BILE
ACIDS**

BACKGROUND

[0001] Miricorilant is a selective, non-steroidal modulator of the glucocorticoid receptor believed to be useful in treating metabolic disorders such as a fatty liver disease (e.g., non-alcoholic steatohepatitis [NASH, also known as metabolic dysfunction-associated steatohepatitis (MASH); these abbreviations are used interchangeably herein], alcoholic fatty liver disease (AFLD), and other fatty liver diseases), antipsychotic induced weight gain (AIWG), and other disorders. Clinical trials regarding miricorilant have been initiated regarding fatty liver disease and AIWG. An alternate named for miricorilant is "CORT118335".

SUMMARY

[0002] Applicant discloses herein pharmacokinetic and metabolic results of miricorilant administration to healthy volunteers and to patients with metabolic dysfunction-associated steatohepatitis (MASH). Miricorilant was safe and was well tolerated in patients with MASH and in healthy volunteers. Patients who respond to miricorilant had a significant enhancement in metabolic clearance of fatty acids (FA)s. The changes are believed to indicate that miricorilant administration may improve metabolic regulation and liver health. For example, the results disclosed herein show that miricorilant is a promising treatment for MASH.

[0003] Applicant discloses herein that patients treated with miricorilant who respond to miricorilant treatment with rapid reduction in liver fat content (LFC) had a significant enhancement in metabolic clearance of fatty acids. Applicant discloses herein that patients treated with miricorilant who respond to miricorilant treatment with efficacy-associated rise in alanine aminotransferase (ALT) levels in their plasma, had a significant enhancement in metabolic clearance of fatty acids. In particular, Applicant discloses herein that patients treated with miricorilant who respond to miricorilant treatment both with rapid reduction in LFC and with an efficacy-associated rise in ALT levels in their plasma, had a significant enhancement in metabolic clearance of fatty acids. Enhancement of metabolic clearance of fatty acids signals improved metabolic regulation and improvement in liver health.

[0004] Patients with presumed MASH treated with miricorilant had rapid liver fat content (LFC) decrease, occasionally accompanied by efficacy-associated alanine aminotransferase (ALT) increase. Responders (defined as patients with an at least 30% decrease in LFC from baseline following miricorilant administration) lost LFC; those responders with rise in plasma ALT levels to greater than three times the upper limit of normal (ULN) lost LFC twice as fast in the first 6 weeks as responders without significant ALT rise. Patients who respond to miricorilant had a significant enhancement in metabolic clearance of fatty acids (FA)s. The changes are believed to indicate that miricorilant administration may improve metabolic regulation and liver health.

[0005] Applicant discloses herein novel methods of enhancing metabolic clearance of fatty acids in patients suffering from fatty liver diseases. The novel methods include administering further once daily doses of miricorilant to patients identified as responding to miricorilant ("miricorilant responder"). A miricorilant responder patient is a patient suffering from an abnormally high baseline liver fat content who has responded to miricorilant administration with a reduction in liver fat content of at least 30% as compared to baseline liver fat content.

[0006] Applicant discloses herein a method of treating a fatty liver disease by administering a further dose of miricorilant to a miricorilant responder patient. Such a further dose of miricorilant may be a further once daily dose of between about 10 milligrams (mg) and 1000 mg miricorilant. Such a further once daily miricorilant dose is effective to provide rapid loss of liver fat content in the patient. The rapid loss of liver fat content, e.g., over six weeks of such once daily miricorilant administration, in a responder patient who has also responded to miricorilant administration with an increase in plasma alanine aminotransferase (ALT) levels to at least three times the upper limit of normal levels of plasma ALT, may be a loss of liver fat content that is twice as fast as the liver fat content loss observed in responder patients whose plasma ALT levels did not increase to at least three times the upper limit of normal levels of plasma ALT. The methods disclosed herein thus enhance metabolic clearance of fatty acids in the miricorilant responder patient, with greater levels of LFC reduction in those responders who have also responded to miricorilant administration with an increase in plasma ALT levels to at least three times the upper limit of normal levels of plasma ALT.

[0007] Applicant further discloses herein pharmacokinetic and metabolic results of miricorilant administration to healthy volunteers and to patients with metabolic dysfunction-associated steatohepatitis (MASH). Miricorilant was safe and was well tolerated in patients with MASH and

in healthy volunteers. Patients who responded to miricorilant had a significant enhancement in metabolic clearance of fatty acids (FA)s. The changes are believed to indicate that miricorilant administration may improve metabolic regulation and liver health.

[0008] Accordingly, Applicant discloses herein that administration of miricorilant to patients suffering from fatty liver disorders, including MASH and other fatty liver disorders, was effective to enhance metabolic clearance of fatty acids, to reduce the plasma level of long-chain fatty acids, to reduce the plasma level of acylglycerols, and to increase the plasma secondary bile acid level in patients suffering from a fatty liver disease. The results indicate that administration of miricorilant provides improved methods of treating patients suffering from fatty liver diseases.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] Fig. 1 shows the concentration of miricorilant in plasma over time following once-daily administration of 150 mg miricorilant for 1 day (circles, lower line), 7 days (squares, middle line), and 14 days (triangles, upper line). Results were from 8 healthy volunteers.

[0010] Fig. 2 shows changes in metabolites from baseline to week 6 in patients with presumed MASH treated with miricorilant. The following abbreviations are found in this figure: 3-hydroxy, 3-hydroxy FA species; β -FAO, beta-fatty acid oxidation; DAG, diacylglycerols; FA, fatty acid; MAG, monoglycerides; ns, non-significant; MUFA, monounsaturated fatty acid; NR, non-responder; PUFA, polyunsaturated fatty acid; RR, rapid responder; SR, standard responder; TAG, triacylglycerols. Statistical analysis: one-way ANOVA vs. NR; matched Sidak multiple comparisons test, with individual variances computed for each comparison.

[0011] Fig. 3 (graph on the left) shows patient liver fat content as measured by magnetic resonance imaging by proton density fat fraction (MRI-PDFF). These data are grouped into three groups: non-responders (NR; left three columns); standard responders (SR; middle three columns); and rapid responders (RR; right three columns). Each responder group has three columns, one for baseline MRI-PDFF (labeled "0"); one for MRI-PDFF results at 6 weeks; and one for MRI-PDFF results at 12 weeks for these patient groups. The graph on the right of Fig. 3 shows the change, at 6 weeks, as compared to baseline in MRI-PDFF for NR, SR, and RR (shown in that order from left-to-right at 6 weeks) and the change, as compared to baseline, in MRI-PDFF for NR and SR at 12 weeks (shown in that order from left-to-right at 12 weeks). Of the 9 RRs, study drug was discontinued in 8 and interrupted in 1 after week 6 due to alanine

amino transferase (ALT) elevation. Two asterisks (**) indicate significance at $P < 0.01$; three asterisks (***) indicate significance at $P < 0.001$; and four asterisks (****) indicate significance at $P < 0.0001$. The dashed line in the figure indicates a 30% reduction from baseline (labelled as -30a); responses at or below that line were $\geq 30\%$ reduced as compared to the baseline response.

[0012] Fig. 4 shows patient cholesterol and triglyceride levels at baseline, at 6 weeks of miricorilant treatment, and at 12 weeks of miricorilant administration, for three groups of patients identified as for non-responders (NR; left-most columns in the groups in both graphs); standard responders (SR; middle-most columns in the groups in both graphs); and rapid responders (RR; right-most columns in the groups in both graphs). Dotted lines indicate baseline mean values for all groups. One asterisk (*) indicates significance at $P \leq 0.05$; two asterisks (**) indicate significance at $P < 0.01$.

[0013] Fig. 5 shows changes in patient acylglycerol levels, as compared to baseline, at week 6 and at week 12 of miricorilant administration. "MAG" indicates monoglyceride; "DAG" indicates diacylglycerol; and "TAG" indicates triacylglycerol. For each of MAG, DAG, and TAG, non-responders are indicated by NR (left-most columns in the groups in both graphs); standard responders are indicated by SR (middle columns in the groups in both graphs); and rapid responders are indicated by RR (right-most columns in the groups in both graphs). Two asterisks (**) indicate significance at $P < 0.01$; four asterisks (****) indicate significance at $P < 0.0001$. "ns" indicates non-significant difference from baseline. Significance was determined by one-way analysis of variance multiple comparisons Dunnett post-test.

[0014] Fig. 6 shows changes in patient long-chain fatty acid (LFCA) levels as compared to baseline at weeks 6 and weeks 12 of miricorilant administration. For each of saturated fatty acids (saturated FAs), monounsaturated fatty acids (MFAs), and polyunsaturated fatty acids (PUFAs), non-responders are indicated by NR (left-most columns in the groups in all three graphs); standard responders are indicated by SR (middle columns in the groups in all three graphs); and rapid responders are indicated by RR (right-most columns in the groups in all three graphs). Two asterisks (**) indicate significance at $P < 0.01$; three asterisks (***) indicate significance at $P < 0.001$; four asterisks (****) indicate significance at $P < 0.0001$. "ns" indicates non-significant difference from baseline. Significance was determined by one-way analysis of variance multiple comparisons Dunnett post-test.

[0015] Fig. 7 shows changes in patient acylcarnitine and in 3-hydroxy fatty acid levels, as compared to baseline, at week 6 and at week 12 of miricorilant administration. Non-responders are indicated by NR (left-most columns in the groups in both graphs); standard responders are indicated by SR (middle columns in the groups in both graphs); and rapid responders are indicated by RR (right-most columns in the groups in both graphs). One asterisk (*) indicates significance at $P \leq 0.05$; “ns” indicates non-significant difference from baseline. Significance was determined by one-way analysis of variance multiple comparisons Dunnett post-test.

[0016] Fig. 8 shows changes in patient bile acid levels, as compared to baseline, at week 6 and at week 12 of miricorilant administration. Non-responders are indicated by NR (left-most columns in the groups in both graphs); standard responders are indicated by SR (middle columns in the groups in both graphs); and rapid responders are indicated by RR (right-most columns in the groups in both graphs). One asterisk (*) indicates significance at $P \leq 0.05$; two asterisks (**) indicate significance at $P < 0.01$; “NS” indicates non-significant difference from baseline. Significance was determined by one-way analysis of variance multiple comparisons Dunnett post-test.

DETAILED DESCRIPTION

[0017] In embodiments, Applicant discloses methods of treating a fatty liver disorder, and methods of enhancing metabolic clearance of fatty acids in a patient in need thereof, said methods comprising administration of miricorilant to a patient in need of treatment for said disorder, where said patient is a responder to miricorilant, wherein a miricorilant responder patient is a patient suffering from an abnormally high baseline liver fat content who has responded to miricorilant administration with a reduction in liver fat content of at least 30% as compared to baseline liver fat content.

[0018] Applicant discloses novel methods of treating a fatty liver disorder, and novel methods of enhancing metabolic clearance of fatty acids in a patient in need thereof, comprising:

Administering, to a miricorilant responder patient,

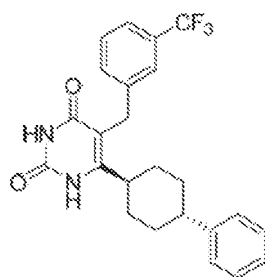
Wherein a miricorilant responder patient is a patient suffering from an abnormally high baseline liver fat content who has responded to miricorilant administration with a reduction in liver fat content of at least 30% as compared to baseline liver fat content,

a further dose of miricorilant,

effective to provide rapid loss of liver fat content in said patient,

Whereby metabolic clearance of fatty acids in the miricorilant responder patient is enhanced. In embodiments, miricorilant doses are once daily miricorilant doses. In embodiments, the further dose of miricorilant is a dose of between about 10 milligrams (mg) and 1000 mg of miricorilant. In embodiments, miricorilant is administered intermittently, e.g., twice per week, or thrice per week, or at other intervals. In embodiments, where said responder patient has responded to miricorilant administration with an increase in plasma alanine aminotransferase (ALT) levels to at least three times the upper limit of normal (ULN) levels of plasma ALT, said rapid loss of liver fat content is a loss of liver fat content over six weeks of said once daily miricorilant administration that is twice as fast as the liver fat content loss observed in responder patients whose plasma ALT levels did not increase to at least three times the ULN levels of plasma ALT.

[0019] Miricorilant is the cyclohexyl pyrimidine compound (E)-6-(4-Phenylcyclohexyl)-5-(3-trifluoromethylbenzyl)-1H-pyrimidine-2,4-dione (“miricorilant”), which has the structure:



. This compound is disclosed in

Example 6, compound 3b of U.S. Patent US 8,685,973. Miricorilant is a selective, non-steroidal modulator of the glucocorticoid receptor believed to be useful in treating metabolic disorders such as a fatty liver disease (e.g., non-alcoholic steatohepatitis [NASH, also known as metabolic dysfunction-associated steatohepatitis (MASH); these abbreviations are used interchangeably herein], alcoholic fatty liver disease (AFLD), and other fatty liver diseases), antipsychotic induced weight gain (AIWG), and other disorders (see, e.g., U.S. Patent 10,238,659; U.S. Patent 10,881,660; U.S. Patent 11,590,135; and U.S. Patent 11,903,945, each of which is hereby incorporated by reference herein in their entireties). Clinical effects of miricorilant are being further investigated in the ongoing MONARCH phase 2b trial (NCT06108219).

[0020] Applicant discloses further novel methods of treating a fatty liver disorder, comprising reducing plasma levels of long-chain fatty acids in a patient suffering from a fatty liver disease, the method comprising:

Administering for at least six weeks,

to a miricorilant responder patient,

Wherein a miricorilant responder patient is a patient suffering from an abnormally high baseline liver fat content who has responded to miricorilant administration with a reduction in liver fat content of at least 30% as compared to baseline liver fat content,

an effective dose of miricorilant, wherein said miricorilant effective dose is effective to:

Reduce polyunsaturated fatty acids in the plasma of the patient by at least about 5 % to about 17 % as compared to baseline levels of polyunsaturated fatty acids, wherein said baseline levels of polyunsaturated fatty acids are determined prior to administration of miricorilant,

Whereby the plasma level of long-chain fatty acids of the miricorilant responder patient is reduced. In embodiments, effective doses of miricorilant are once daily miricorilant doses. In embodiments, effective doses of miricorilant are administered intermittently, e.g., twice per week, or thrice per week, or at other intervals.

[0021] Applicant discloses further novel methods of treating a fatty liver disorder, comprising reducing plasma levels of acylglycerols in a patient suffering from a fatty liver disease, the method comprising:

Administering for at least six weeks,

to a miricorilant responder patient,

Wherein a miricorilant responder patient is a patient suffering from an abnormally high baseline liver fat content who has responded to miricorilant administration with a reduction in liver fat content of at least 30% as compared to baseline liver fat content,

an effective dose of miricorilant, wherein said miricorilant effective dose is effective to:

Reduce levels of acylglycerols in the plasma of the patient by about 25 % as compared to baseline levels of acylglycerols, wherein said baseline acylglycerol levels are determined prior to administration of miricorilant,

Whereby the plasma level of acylglycerols of the miricorilant responder patient is reduced. In embodiments, effective doses of miricorilant are once daily miricorilant doses. In

embodiments, effective doses of miricorilant are administered intermittently, e.g., twice per week, or thrice per week, or at other intervals.

[0022] Applicant discloses further novel methods of treating a fatty liver disorder, comprising increasing the plasma secondary bile acid level in a patient suffering from a fatty liver disease, the method comprising:

Administering for at least six weeks,

to a miricorilant responder patient,

Wherein a miricorilant responder patient is a patient suffering from an abnormally high baseline liver fat content who has responded to miricorilant administration with a reduction in liver fat content of at least 30% as compared to baseline liver fat content,

an effective dose of miricorilant, wherein said miricorilant effective dose is effective to: increase the level of secondary bile acids in the plasma of the patient by about 35 % as compared to the baseline plasma secondary bile acid level, wherein said baseline plasma secondary bile acid level is determined prior to administration of miricorilant,

Whereby the plasma level of secondary bile acids of the miricorilant responder patient is increased. In embodiments, effective doses of miricorilant are once daily miricorilant doses. In embodiments, effective doses of miricorilant are administered intermittently, e.g., twice per week, or thrice per week, or at other intervals. In embodiments, where said responder patient has responded to miricorilant administration with an increase in plasma alanine aminotransferase (ALT) levels to at least three times the upper limit of normal (ULN) levels of plasma ALT, said loss of long-chain fatty acid, or of acylglycerol, or of secondary bile acid content is a loss that is twice as fast as the liver fat content loss observed in responder patients whose plasma ALT levels did not increase to at least three times the ULN levels of plasma ALT.

[0023] In embodiments, miricorilant is administered orally. In embodiments, miricorilant, is administered on a daily basis; for example, in embodiments, miricorilant is administered once per day. In embodiments, miricorilant, is administered every other day, or every third day, or two times per week, or three times per week, or once per week, or intermittently on another administration schedule. In embodiments, miricorilant is administered with food. Administered “with food” means that the patient has begun eating a meal within 30 minutes, or within one hour, of the time that miricorilant is administered. For example, miricorilant may be

administered to a patient with a meal, or soon after (e.g., within half an hour) the patient began eating the meal.

[0024] In alternative embodiments, miricorilant is administered to a fasted patient, i.e., to a patient who has not eaten food for at least one hour, or at least two hours, or more hours prior to miricorilant administration. For example, miricorilant may be administered to a fasted patient in the morning, i.e., to a patient who has not yet eaten the morning meal, and has not eaten since the evening meal of the prior evening.

[0025] In embodiments, miricorilant is administered daily, or every other day, or every third day, or two times per week, or three times per week, or once per week, or on another intermittent administration schedule, at a daily dose of miricorilant of between about 1 and 30 mg/kg/day, preferably a daily dose of miricorilant of between about 1 and 20 mg/kg/day. In embodiments, the daily dose of miricorilant is between about 10 and about 2000 milligrams (mg), or between about 50 and about 1500 mg, or between about 100 and about 1000 mg miricorilant. In embodiments, a daily dose of miricorilant may be about 10 mg, or 15 mg, or 20 mg, or 25 mg, or 50 mg, or 75 mg, or 100 mg, or 125 mg, or 150 mg, or 175 mg, or 200 mg, or 225 mg, or 250 mg, or 275 mg, or 300 mg, or 325 mg, or 350 mg, or 375 mg, or 400 mg, or 450 mg, or 500 mg, or 550 mg, or 600 mg, or 650 mg, or 700 mg, or 750 mg, or 800 mg, or 850 mg, or 900 mg, or 950 mg of miricorilant. In embodiments, an effective dose of miricorilant is between 10 milligrams per day (mg/day) and 200 mg/day, and may be selected from 10 mg per day, 20 mg/day, 30 mg/day, 40 mg/day, 50 mg/day, 75 mg/day, 100 mg/day, 120 mg/day, 125 mg/day, 150 mg/day, 175 mg/day, 200 mg/day, 250 mg/day, 300 mg/day, 350 mg/day, 400 mg/day, 450 mg/day, 500 mg/day, 550 mg/day, 600 mg/day, 650 mg/day, 700 mg/day, 750 mg/day, 800 mg/day, 850 mg/day, 900 mg/day, and 950 mg per day. In embodiments, the effective dose of miricorilant is 50 mg/day, 100 mg/day, 125 mg/day, 150 mg/day, 200 mg/day, 250 mg/day, 300 mg/day, 350 mg/day, 400 mg/day, 450 mg/day, 500 mg/day, 550 mg/day, 600 mg/day, 650 mg/day, 700 mg/day, 750 mg/day, 800 mg/day, 850 mg/day, 900 mg/day, or 950 mg/day. In embodiments where miricorilant is administered intermittently, these doses described as “mg/day” refer to the dose administered on a day in which miricorilant is administered to the patient. In embodiments, an effective miricorilant dose for treatment of a fatty liver disease such as, e.g., NASH, or a disorder associated with obesity or a fatty liver disease, is between about 10

mg/day and about 1000 mg/day, and may be, e.g., 10 mg/day, 20 mg/day, 30 mg/day, 40 mg/day, 50 mg/day, 75 g/day, 80 mg/day, 100 mg/day, 125 mg/day, 150 mg/day, 200 mg/day, 250 mg/day, 300 mg/day, 350 mg/day, 400 mg/day, 450 mg/day, 500 mg/day, 550 mg/day, 600 mg/day, 650 mg/day, 700 mg/day, 750 mg/day, 800 mg/day, 850 mg/day, 900 mg/day, or 950 mg/day. In embodiments, an effective miricorilant dose for treatment of antipsychotic-induced weight gain (AIWG) is between about 10 mg/day and about 950 mg/day, and may be, e.g., 10 mg/day, 20 mg/day, 30 mg/day, 40 mg/day, 50 mg/day, 75 g/day, 80 mg/day, 100 mg/day, 125 mg/day, 150 mg/day, 200 mg/day, 250 mg/day, 300 mg/day, 350 mg/day, 400 mg/day, 450 mg/day, 500 mg/day, 550 mg/day, 600 mg/day, 650 mg/day, 700 mg/day, 750 mg/day, 800 mg/day, 850 mg/day, 900 mg/day, or 950 mg/day. In embodiments, the miricorilant dose may be adjusted (e.g., increased as needed, or decreased if indicated) from an initial dose during the course of treatment.

DEFINITIONS

[0026] As used herein, the term “about”, e.g., as used in the phrase “about X” where X is a numerical value, is used to indicate a range of $\pm 10\%$ of the named value of X.

[0027] As used herein, the term “substantially”, e.g., as used in the phrase “X is substantially the same as Y” refers to a value of X that is within about 30%, or within about 25%, or within about 20%, or within about 15%, or within about 10% of the value of the term Y. When referring to a time, e.g., the phrase “substantially the same time as X” refers to a time that is within about 15 minutes of time X; or, e.g., when referring to a second event occurring at “substantially the same time” as a first event, the two events occur within about 15 minutes of each other.

[0028] As used herein, the term “patient” refers to a human that is or will be receiving, or has received, medical care for a disease or condition.

[0029] As used herein, the terms “administer,” “administering,” “administered” or “administration” refer to providing a compound or a composition (e.g., one described herein), to a subject or patient. Administration may be by oral administration (i.e., the subject receives the compound or composition via the mouth, as a pill, capsule, liquid, or in other form suitable for administration via the mouth). Oral administration typically involves swallowing the pill, capsule, liquid, or other formulation. Oral administration may include buccal administration

(where the compound or composition is held in the mouth, e.g., under the tongue, and absorbed there).

[0030] Other examples of modes of administration include, e.g., by injection, i.e., delivery of the compound or composition via a needle, microneedle, pressure injector, or other means of puncturing the skin or forcefully passing the compound or composition through the skin of the subject. Injection may be intravenous (i.e., into a vein); intraarterial (i.e., into an artery); intraperitoneal (i.e., into the peritoneum); intramuscular (i.e., into a muscle); or by other route of injection. Routes of administration may also include rectal, vaginal, transdermal, via the lungs (e.g., by inhalation), subcutaneous (e.g., by absorption into the skin from an implant containing the compound or composition), or by other route.

[0031] As used herein, the term “effective amount” or “therapeutic amount” refers to an amount of a pharmacological agent effective to treat, eliminate, or mitigate at least one symptom of the disease being treated. In some cases, “therapeutically effective amount” or “effective amount” can refer to an amount of a functional agent or of a pharmaceutical composition useful for exhibiting a detectable therapeutic or inhibitory effect. The effect can be detected by any assay method known in the art.

[0032] As used herein, the term “pharmaceutically acceptable carrier” is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. Therapeutic agents typically may be orally administered in capsules, tablets, or other formulations which include the active agent and one or more pharmaceutically acceptable carriers. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active agents can also be incorporated into the compositions.

[0033] “Liver disorder unrelated to excessive ingestion of alcohol” is a liver disorder that is distinguished from alcohol related liver disease (ARLD). Such a disorder therefore refers to a wide array of liver diseases that are not caused by alcohol consumption. For example, hepatitis can be caused by viral infection. A liver disorder caused by excessive alcohol consumption and other factors, is considered an ARLD rather than a liver disorder unrelated to excessive ingestion

of alcohol. In contrast, a liver disorder merely exacerbated by excessive alcohol consumption is considered a liver disorder unrelated to excessive ingestion of alcohol.

[0034] “Nonalcoholic fatty liver disease” or “NAFLD” refers to a fatty liver disease characterized by the presence of fat (lipids) in the liver and no substantial inflammation or liver damage. NAFLD can progress into metabolic dysfunction-associated steatohepatitis (MASH) (MASH was formerly known as nonalcoholic steatohepatitis (NASH)), and then into irreversible, advanced liver scarring or cirrhosis.

[0035] As used herein, the term “MASH” refers to Metabolic Dysfunction-Associated Steatohepatitis, and the term “NASH” refers to non-alcoholic steatohepatitis. The newer term MASH is now used in place of the older term NASH, but both terms refer to the same group of liver disorders and associated symptoms of those liver disorders (thus, for example, the disorder is sometimes referred to as MASH/NASH). Both MASH and NASH refer to a fatty liver disease which resembles alcoholic liver disease, but occurs in people who drink little or no alcohol. The major feature in MASH/NASH is fat in the liver, along with inflammation and damage. MASH can lead to cirrhosis, in which the liver is permanently damaged and scarred and is no longer able to function properly. A differential diagnosis of MASH versus NAFLD may be determined by liver biopsy.

[0036] As used herein, the term “MRI-PDFF” refers to magnetic resonance imaging by proton density fat fraction.

[0037] As used herein, the term “AUC” refers to the area under the plasma concentration-time curve calculated using the linear up/log down trapezoidal method.

[0038] As used herein, the terms “AUC_{0-tau}” and “AUC_(0-tau)” refer to the AUC from time zero to time tau.

[0039] As used herein, the terms “AUC₀₋₂₄” and “AUC₍₀₋₂₄₎” refer to the AUC from time zero to hour 24 post dose.

[0040] As used herein, the terms “AUC_{0-inf}” and “AUC_(0-inf)” refer to the AUC from time 0 to extrapolated to infinity.

[0041] As used herein, the terms “AUC_{0-last}” and “AUC_(0-last)” refer to the AUC from time 0 to time of the last measurable concentration (C_{last}).

[0042] As used herein, the term “BCRP” refers to breast cancer resistance protein.

[0043] As used herein, the term “BIW” refers to twice per week, as in twice weekly drug administration.

[0044] As used herein, the term “BMI” refers to body mass index.

[0045] As used herein, the term “QD” refers to once daily, as in once daily drug administration.

[0046] As used herein, the term “CI” refers to confidence interval.

[0047] As used herein, the term “C_{last}” refers to the last measurable concentration of the analyte.

[0048] As used herein, the term “C_{max}” refers to the maximum observed plasma concentration of the analyte.

[0049] As used herein, the term “CV” refers to coefficient of variance.

[0050] As used herein, the term “CV%” refers to coefficient of variation expressed as a percent.

[0051] As used herein, the term “GM” refers to geometric mean.

[0052] As used herein, the term “G-CV%” refers to geometric coefficient of variance (in %).

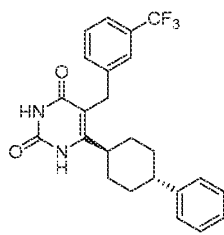
[0053] As used herein, the term “GMR” refers to adjusted geometric mean ratio.

[0054] As used herein, the term “plasma clearance” refers to the removal of a substrate from the blood of a subject to whom the substrate has been administered. Plasma clearance may be reported as a percentage or fraction of the original amount of substrate removed from the blood as a function of time since administration; or may be reported as the time for the amount of substrate to be reduced to half the original amount (e.g., as a half-time (t_{1/2})).

[0055] As used herein, the terms “enzyme activity”, and “activity” (when referring to an enzyme) refer to the activity of an enzyme in metabolizing an enzyme substrate. Enzyme activity may be measured, for example, by providing the enzyme with its enzyme substrate, and measuring the metabolic conversion of that substrate. Enzyme activity may be measured in intact animals or subjects; in tissue preparations (e.g., isolated liver or liver portions); in tissue homogenates (e.g., liver microsomes); in cell culture; and by other *in vivo* and *in vitro* methods.

In an animal possessing that enzyme, plasma AUC values, or plasma clearance of that substrate, may be used to determine enzyme activity.

[0056] Miricorilant ((E)-6-(4-Phenylcyclohexyl)-5-(3-trifluoromethylbenzyl)-1H-pyrimidine-2,4-dione) is a mixed agonist/antagonist of the glucocorticoid receptor. Miricorilant has the structure:



Miricorilant is described in Example 6, compound 3b of U.S. 8,685,973 (hereby incorporated by reference).

EXAMPLE 1 Pharmacokinetics (PK) and metabolism of miricorilant

[0057] Miricorilant is an oral, nonsteroidal selective glucocorticoid receptor (GR) modulator (SGRM) that acts as a mixed agonist/antagonist of the GR and a modest antagonist of the mineralocorticoid receptor. Metabolic elimination of miricorilant is primarily by CYP2C19. Miricorilant is in development for the treatment of metabolic dysfunction-associated steatohepatitis (MASH). In a phase 1b study of patients with presumed MASH, miricorilant 100 mg twice weekly was safe, well tolerated, reduced liver fat content, and improved hepatic, glycemic, and lipid markers (Alkhouri N et al. *Hepatology*. 2023;78(S1):S1-S2154). Over 450 patients and healthy volunteers have received miricorilant in clinical trials to date. This Example describes the pharmacokinetics (PK) and metabolism of miricorilant in several non-clinical and phase 1 clinical development trials.

[0058] **Methods:** Tissue distribution of oral [^{14}C]-miricorilant 50 milligrams per kilogram (mg/kg) was assessed in male albino mice (n=7; timepoints: 1, 4, 8, 12, 24, 72, and 168 hours) and in partially pigmented mice (n=4; timepoints: 1, 24, 72, and 168 hours).

[0059] Study 850 (NCT03315338) was a first-in-human, double-blind, randomized, placebo-controlled study testing multiple ascending doses (150–900 mg) of oral miricorilant for 14 days in fasted healthy volunteers (18–60 years; BMI 18–30 kg/m²). The multiple ascending doses cohort received 150 – 900 mg of oral miricorilant (administered fasted) for 14 days. The food

effect cohort received 900 mg of oral miricorilant (administered fasted); a minimum of 7 days later, 900 mg of oral miricorilant was administered after a high-fat breakfast. PK and safety were assessed.

[0059] Study 851 (NCT03878264) evaluated the absorption, distribution, metabolism, and excretion (ADME) and mass balance of a single oral dose of [^{14}C]-miricorilant 150 mg (administered fed) in healthy male volunteers (30—65 years; BMI 18—30 kg/m²). PK and safety were assessed.

[0060] Study 854 (NCT05553470) was an open-label, adaptive design study of single-dose miricorilant 600 mg given under fed conditions in patients with moderate hepatic impairment compared to healthy volunteers with normal hepatic function; PK and safety were assessed.

[0061] Study 861 (NCT05117489) was a phase 1b, open-label trial of adult patients with presumed MASH that included 11 cohorts of patients who received miricorilant doses ranging from 30–200 mg intermittently or daily for 12 or 24 weeks; PK was assessed under fed conditions. Efficacy, safety, and PK were assessed.

[0062] **Results:** Overall, miricorilant was safe and well tolerated in patients with MASH and in healthy volunteers, with most treatment emergent adverse events (TEAEs) being mild (grade ≤ 2). Safety results in the phase 1b study of patients with MASH have been previously presented (Alkhoury et al. *Hepatology* 2023;78(S1):S1-S2154.) Across these studies, 205 healthy volunteers received miricorilant. No serious TEAEs related to miricorilant were reported in healthy volunteers. No significant safety signals were identified.

[0063] High levels of radioactivity were present in the liver 1, 4, and 8 hours following oral administration of [^{14}C]-miricorilant in albino mice. In pigmented mice, radioactivity was not present at quantifiable levels in melanin-containing tissues (skin and uveal tract).

[0064] In study 850, systemic concentrations increased with repeated dosing with miricorilant 150 mg daily for 14 days in healthy volunteers (n = 8). Steady state plasma exposures were achieved by Day 7, resulting in an overall accumulation ratio from Days 1 to 14 of 1.68 for C_{max} and 2.17 for AUC_(0-tau), with an elimination half-life of 21.6 hours. Miricorilant was generally well tolerated in healthy volunteers. In study 851, following administration of a single oral dose of [^{14}C]-miricorilant 150 mg to healthy volunteers (n = 6), 89.1% of the total radioactivity was

recovered in the feces, with minimal recovery in the urine (<5%), suggesting that the predominant route of elimination is hepatic. Miricorilant accounted for 57.7% of the total radioactivity in plasma based on $AUC_{(0-inf)}$ (ratio of 0.577), indicating that parent miricorilant was the main circulating species in plasma following oral administration (see FIG. 1).

[0065] Repeated once-daily administration of doses of miricorilant in the absence of other compounds were investigated. Fig. 1 shows the concentration of miricorilant in plasma over time following once-daily administration of 150 mg miricorilant for 1 day (circles, lower line), 7 days (squares, middle line), and 14 days (triangles, upper line). Results were from 8 healthy volunteers. Measurements of C_{max} and $AUC_{(0-24)}$ from days 1, 7, and 14 are presented in Table 1. ($AUC_{(0-24)}$, area under the curve from time 0 to 24 hours; C_{max} , maximum measured concentration; CV%, coefficient of variation.) Steady state plasma exposures were achieved by Day 7, resulting in overall accumulation ratios from Days 1 to 7 of 1.42 for C_{max} and 1.92 for $AUC_{(0-24)}$. Accumulation ratios for Days 1 to 14 were 1.68 for C_{max} and 2.17 for $AUC_{(0-24)}$, with an elimination half-life of 21.6 hours.

TABLE 1 MIRICORILANT EXPOSURE (150 mg DOSE)

	Miricorilant 150 mg		
Geometric mean (geometric CV%)	Day 1	Day 7	Day 14
C_{max} (ng/mL)	100 (38.2)	142 (63.5)	169 (30.1)
$AUC_{(0-24)}$ (ng•h/mL)	896 (38.3)	1730 (44.7)	1940 (39.2)

[0066] Following miricorilant dosing at 100, 300 and 900 mg, exposure increased in a close to dose-proportional manner based on C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-inf)}$. Miricorilant plasma exposures were approximately 3-fold higher following administration of miricorilant 900 mg under fed vs fasted conditions ($AUC_{(0-last)}$): 25,200 ng•h/mL vs 7,640 ng•h/mL).

[0067] The plasma concentrations of miricorilant over time following administration of 600 mg miricorilant in individual subjects were measured. The ratios of AUC_{0-inf} measured on day 10 compared to AUC_{0-inf} measured on day 1 ranged from 1.28 to 4.49, with an average value of 2.18 (n = 26).

[0068] In study 854, effects of hepatic impairment on the pharmacokinetics (PK) of miricorilant were studied in a Phase 1, open-label, adaptive design study (NCT05553470). In this study, adult

patients with moderate hepatic impairment (Child-Pugh Class B; including patients with MASH) were matched with healthy volunteers based on gender, age (± 10 years), and weight ($\pm 20\%$). Ten healthy volunteers and 10 patients with hepatic impairment (including 4 patients with MASH) were enrolled. All participants received a single oral dose of miricorilant 600 mg under fed conditions. Plasma concentrations of miricorilant were determined with a validated LC-MS/MS bioanalytical method at pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, and 24 hours post-dose, then daily through day 7. Safety and tolerability were monitored throughout the study.

[0069] Pharmacokinetic (PK) results for each cohort are shown in Table 2. The observed effect of moderate hepatic impairment on miricorilant PK was small. Following a single dose of 600 mg miricorilant, the geometric mean ratios (90% CI) of miricorilant $AUC_{0-\infty}$ and C_{max} were 133% (97.9%–179.9%) and 82% (65.7%–101.5%), respectively, in patients with hepatic impairment compared to healthy matched volunteers. The half-life of miricorilant was 25.5 and 36.0 hours in healthy matched volunteers and patients with hepatic impairment, respectively. No grade ≥ 3 adverse events or laboratory abnormalities were observed in either group, and no new safety concerns were identified. There was no apparent difference in plasma exposures in patients with moderate hepatic impairment ($n = 10$) compared to healthy volunteers ($n = 10$) with normal hepatic function.

TABLE 2

PK parameters of 600 mg miricorilant in patients with hepatic impairment and healthy matched volunteers

	Healthy Volunteers GM (%CV) N=10	Patients with Hepatic Impairment GM (%CV) N=10	GMR vs Healthy Volunteers % (90% CI)
$AUC_{(0-\infty)}$ (ng·h/mL)	11,619 (44.09)	15,420 (37.33)	133 (97.9–179.9)
$AUC_{(0-last)}$ (ng·h/mL)	11,317 (43.09)	14,326 (35.79)	127 (94.1–170.1)
C_{max} (ng/mL)	708.8 (26.22)	578.7 (30.97)	82 (65.7–101.5)

%CV, coefficient of variation; $AUC_{0-\infty}$, area under the curve from time 0 extrapolated to infinity; $AUC_{(0-last)}$, area under the curve from time 0 to the time of last measurable concentration; CI, confidence interval; C_{max} , maximum measured concentration; GM, geometric mean; GMR, ratio of geometric mean; PK, pharmacokinetic.

[0070] **Conclusions of Study 854:** Miricorilant 600 mg was generally well tolerated in patients with hepatic impairment and in matched healthy volunteers. Moderate hepatic impairment had minimal impact on the PK profile of miricorilant.

[0071] In study 861 (a phase 1b study in patients with presumed MASH), miricorilant plasma PK behaved in an approximately dose proportional manner across the range of miricorilant doses and dosing regimens evaluated in patients with MASH (n = 71). As noted above, this study included 11 cohorts of patients who received miricorilant doses ranging from 30—200 mg intermittently or daily for 12 or 24 weeks; PK was assessed under fed conditions.

TABLE 3 Steady state PK in patients receiving daily miricorilant 100 mg

All patients received daily miricorilant 100 mg during the phase 1b PK analysis.

QD dose (100 mg)	C _{max} (ng/mL) N = 18	AUC ₍₀₋₂₄₎ (ng·h/mL) N = 13
Geometric Mean (Geometric CV%) [median range]	170 (151) [207 (4.4 – 610)]	4148 (40.8) [4262 (1672 – 7416)]

TABLE 4 PK in patients receiving twice-weekly miricorilant 100 mg

All patients received twice-weekly miricorilant 100 mg during the phase 1b PK analysis.

BIW dose (100 mg)	C _{max} (ng/mL) N = 13	AUC ₍₀₋₂₄₎ (ng·h/mL) N = 11
Geometric Mean (Geometric CV%) [median range]	98.0 (130) [114 (8.1 – 346)]	1337 (49.7) [1135 (898 – 4294)]

Twice per week: BIW

[0072] **SUMMARY** These studies characterize the pharmacokinetics and absorption, distribution, metabolism, and excretion (PK/ADME) of miricorilant. Administration of [¹⁴C]-miricorilant to mice resulted in high concentrations of radioactivity in the liver. The primary route of miricorilant elimination is hepatic. Miricorilant systemic concentrations increased with repeated daily dosing, with accumulation ratios of 1.42 for C_{max} and 1.92 for AUC₍₀₋₂₄₎ and steady state exposures achieved by Day 7. Miricorilant is a strong inhibitor of CYP2C8 *in vivo*. Miricorilant is a moderate inhibitor of BCRP *in vivo*. Miricorilant does not affect the activity of UGT1A1, CYP3A4, or CYP2C9 *in vivo*. In patients with presumed MASH, miricorilant plasma PK behaved in an approximately dose proportional manner. Miricorilant was well tolerated in patients and healthy volunteers.

EXAMPLE 2**Effect of Hepatic Impairment on the Pharmacokinetics of Miricorilant: Results from a Phase 1, Open-Label, Adaptive-Design Study**

[0073] **Background and Aims:** Miricorilant is a nonsteroidal selective glucocorticoid receptor modulator (SGRM) that acts as a mixed agonist/antagonist of the GR and a modest antagonist of the mineralocorticoid receptor. Miricorilant is currently being evaluated in the phase 2 MONARCH trial (NCT06108219) for the treatment of noncirrhotic (stages F1–3) metabolic dysfunction-associated steatohepatitis (MASH). In a previous phase 1b trial, patients (pts) with presumed MASH treated with twice-weekly miricorilant 100 mg had a reduction in liver fat content as well as improvements in hepatic, lipid, and glycemic markers (Alkhoury et al. *Hepatology* 2024). As the primary route of elimination for miricorilant is hepatic (Custodio et al. *EASL* 2024), our objective here was to evaluate the effect of hepatic impairment on the pharmacokinetic (PK) profile of miricorilant.

[0074] **Methods:** In this phase 1, open-label, adaptive-design study (NCT05553470), adult patients with moderate (Child-Pugh Class B; including patients with MASH) or severe (Child-Pugh Class C) hepatic impairment were matched with healthy control volunteers based on gender, age (± 10 years), and weight ($\pm 20\%$). All participants received a single oral dose of miricorilant 600 mg under fed conditions. Plasma concentrations of miricorilant were determined with a validated LC-MS/MS bioanalytical method at pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 48, 72, 96, 120, and 144 hours post-dose. Safety and tolerability were monitored throughout the study.

[0075] **Results:** The study enrolled patients with moderate hepatic impairment (n=10, including 4 patients with MASH), severe hepatic impairment (n=9), and healthy volunteers (n=10). The observed effect of moderate and severe hepatic impairment on miricorilant PK was small. Following a single dose of miricorilant, the geometric mean ratios (90% CI) of miricorilant AUC_{0-inf} and C_{max} were 133% (97.9–179.9%) and 82% (65.7–101.5%), respectively, in patients with moderate hepatic impairment compared to healthy matched volunteers. The geometric mean ratios (90% CI) of miricorilant AUC_{0-inf} and C_{max} were 136% (91.4–202.6%) and 30% (24.2–37.5%), respectively, in patients with severe hepatic impairment compared to healthy matched volunteers. The half-life of miricorilant in patients with moderate and severe hepatic impairment

was 36.0 and 76.7 hours, respectively, as compared with a half-life of 25.5 hours in healthy matched volunteers. No grade ≥ 3 adverse events or laboratory abnormalities were observed, and no new safety concerns were identified.

TABLE 5**Summary of Statistical Comparisons of Plasma Pharmacokinetic Parameters**

Analyte	Population	Parameter (units)	Impaired ¹ (test)		Control ¹ (reference)		Ratio of Geo. LS Means (%)	90% CI (%)	Inter-Subject CV%
			n	Geo. LS Mean	n	Geo. LS Mean			
CORT118335	Healthy vs. Moderate HI	AUC _{0-inf} (h*ng/mL)	10	15420	10	11620	132.72	97.89 - 179.93	40.81
		AUC ₀₋₄ (h*ng/mL)	10	14330	10	11320	126.58	94.18 - 170.14	39.56
		C _{max} (ng/mL)	10	578.7	10	708.8	81.65	65.65 - 101.54	28.68
	Healthy vs. Severe HI	AUC _{0-inf} (h*ng/mL)	9	15810	10	11620	136.09	91.40 - 202.63	53.05
		AUC ₀₋₄ (h*ng/mL)	9	11110	10	11320	98.15	69.53 - 138.56	45.22
		C _{max} (ng/mL)	9	213.5	10	708.8	30.12	24.17 - 37.53	28.05
CORT118335-P9	Healthy vs. Moderate HI	AUC _{0-inf} (h*ng/mL)	10	6206	10	1614	384.54	238.68 - 619.53	67.80
		AUC ₀₋₄ (h*ng/mL)	10	5402	10	1508	358.22	224.35 - 571.98	66.27
		C _{max} (ng/mL)	10	115.4	10	93.94	122.86	93.22 - 161.92	36.76
	Healthy vs. Severe HI	AUC _{0-inf} (h*ng/mL)	9	9126	10	1614	565.45	291.54 - 1096.70	99.37
		AUC ₀₋₄ (h*ng/mL)	9	4535	10	1508	300.77	188.42 - 480.11	63.90
		C _{max} (ng/mL)	9	52.40	10	93.94	55.79	42.88 - 72.58	33.84

¹Control=healthy control, Impaired=moderate or severe hepatic impairment (Child-Pugh Class B)

CV%=Coefficient of Variation; Geo.=Geometric; LS=Least Squares; CI=Confidence Interval

A model was performed with natural log-transformed PK parameters as the dependent variables and hepatic function as a fixed effect.

[0076] Conclusions: Miricorilant 600 mg was generally well tolerated in patients with moderate and severe hepatic impairment and in matched healthy volunteers. Hepatic impairment had minimal impact on the systemic plasma exposures (as measured by AUC) of miricorilant. These findings support future inclusion of patients with compensated cirrhotic (stage F4) MASH in the miricorilant clinical development program.

EXAMPLE 3 Metabolomic and Lipidomic Analysis of Patients with Presumed MASH

[0077] The aim of this metabolomics study was to explore the mechanism by which miricorilant reduces liver fat.

[0078] Plasma samples were collected from a phase 1b, open-label trial (NCT05117489) of adult patients with MASH who received 30 mg to 200 mg of miricorilant intermittently or daily for 12 or 24 wks. Samples were grouped as: standard responders (SR) without alanine amino transferase (ALT) rise (n=11); rapid responders (RR) with ALT rise greater than three times the upper limit of normal (>3x ULN) (n=9); and non-responders (NR, minimal changes in liver fat content (LFC) from baseline (BL; n=11). Changes in serum metabolomics profiles were assessed at different time points by liquid chromatography/mass spectrometry (Metabolon). Patient characteristics (prior to study treatments) are presented in Table 6. Results of these studies are presented in Figs. 2 - 8.

Table 6 Baseline Patient Characteristics

	SRs (n=11)	RRs (n=9)	NRs (n=11)
Age group, n (%)			
<30 y	0	0	2 (18.2)
30 to 50 y	4 (36.4)	4 (44.4)	3 (27.3)
>50 y	7 (63.6)	5 (55.6)	6 (54.5)
Female, n (%)	7 (63.6)	5 (55.6)	6 (54.5)
Race, n (%)			
White	11 (100)	8 (88.9)	11 (100)
Asian	0	1 (11.1)	0
Hispanic or Latino ethnicity, n (%)	7 (63.6)	5 (55.6)	6 (54.5)
BMI, n (%)			
30 to <35 kg/m ²	2 (18.2)	5 (55.6)	4 (36.4)
35 to <40 kg/m ²	4 (36.4)	1 (11.1)	4 (36.4)
≥40 kg/m ²	4 (36.4)	2 (22.2)	2 (18.2)
Liver stiffness, n (%)		(n=8)	
8.5 to 12 kPa	6 (54.5)	4 (50.0)	10 (90.9)
>12 kPa	5 (45.4)	4 (50.0)	1 (9.1)
MRI-PDFF %, mean (SD)	18.7 (6.7)	20.3 (6.7)	17.9 (5.6)
Hypertension, n (%)	5 (45.4)	5 (55.6)	7 (63.6)
Diabetes, n (%)	7 (63.6)	2 (22.2)	3 (27.3)

BMI, body mass index; MRI-PDFF, magnetic resonance imaging derived proton density fat fraction; NR, nonresponder; RR, rapid responder; SD, standard deviation; SR, standard responder.

[0079] Fig. 3 shows patient liver fat content as measured by MRI-PDFF. The graph on the left of Fig. 3 shows liver fat content at baseline (labeled "0"), and patient responses at 6 weeks and 12 weeks of treatment for the three groups of patients: non-responders (NR), standard responders (SR), and rapid responders (RR). Of the 9 RRs, study drug was discontinued in 8 and interrupted in 1 after week 6 due to alanine amino transferase (ALT) elevation. The graph on the right of Fig. 3 shows the change, at 6 weeks, as compared to baseline in MRI-PDFF for NR, SR, and RR (shown in that order from left-to-right at 6 weeks) and the change, as compared to baseline, in MRI-PDFF for NR and SR at 12 weeks (shown in that order from left-to-right at 12 weeks). Two asterisks (**) indicate significance at $P < 0.01$; three asterisks (***) indicate significance at $P < 0.001$; and four asterisks (****) indicate significance at $P < 0.0001$. The dashed line in the figure indicates a 30% reduction from baseline (labelled as -30a); responses at or below that line were $\geq 30\%$ reduced as compared to the baseline response. As shown in Fig. 3, both SR and RR patients experienced significant reductions in liver fat content at 6 weeks as compared to baseline liver fat content, and SR patients experienced significant reductions in liver fat content at 12 weeks as compared to baseline liver fat content. (No results are reported at 12 weeks for RR patients due to discontinuation or interruption of study drug administration in those patients).

[0080] Patient cholesterol and triglyceride levels are shown in Fig. 4 at baseline, at 6 weeks of miricorilant treatment, and at 12 weeks of miricorilant administration, for three groups of patients identified as for non-responders (NR; left-most columns in the groups in both graphs); standard responders (SR; middle columns in the groups in both graphs); and rapid responders (RR; right-most columns in the groups in both graphs). Dotted lines indicate baseline mean values for all groups. One asterisk (*) indicates significance at $P \leq 0.05$; two asterisks (**) indicate significance at $P < 0.01$. Rapid responders showed significant reductions in cholesterol ($P < 0.05$) and in triglyceride ($P < 0.01$) levels at 6 weeks of treatment as compared to baseline levels of cholesterol and triglycerides.

[0081] Both groups of responders showed notably lower levels of acylglycerols such as triacylglycerols at week 6 compared to non-responders (NR) (standard responders (SR): +2.6%, $P < 0.0001$; rapid responders (RR): -26.8%, $P < 0.0001$; vs NR: +10.8%). Most long-chain fatty acids (FAs), including polyunsaturated FAs (omega-3 and -6), were significantly reduced at week 6 as compared to baseline (BL) in both responder groups (SR: -5.3%, $P < 0.01$; RR: -16.6%, $P < 0.0001$), with minimal changes in NRs (+0.6%, non-significant [ns]). Many short- to medium-

chain acylcarnitine species were reduced in RRs as compared to NRs (-3.3% at week 6, ns). Several 3-hydroxy FA species were reduced in RRs as compared to NRs at week 6 (-12.7% from BL, $P<0.05$). RRs trended towards elevated bile acids as compared to NRs at week 6 (+21.5%, $P=0.06$). Secondary bile acids were significantly increased at week 6 in RRs but not in SRs (RR: +34.6%, $P<0.05$; SR: +17.3%, ns; from BL).

[0082] These results are illustrated in Figs. 5 – 8 (acylglycerol levels: Fig. 5; long-chain fatty acid levels: Fig. 6; acylcarnitine and 3-hydroxy fatty acid levels: Fig. 7; bile acid levels: Fig. 8) and tabulated in the following Tables.

TABLE 7 Fold Changes in Acylglycerol Levels From Baseline to Week 6 and Week 12

Week 12a Biochemical Name / Ratio	NR		SR		RR	
	Wk6/BL	Wk12/BL	Wk6/BL	Wk12/BL	Wk6/BL	Wk12/BL
DAG (16:0/16:0)	1.10	1.14	0.71	0.84	0.88	0.51
DAG (16:0/18:0)	1.03	1.03	0.40	0.85	0.74	0.33†
DAG (16:0/22:5)	1.07	1.25	0.98	0.96	0.73†	0.49†
TAG 52:5-FA14:0	1.07	1.13	0.96	0.91	0.70†	0.66†
TAG 52:5-FA22:5	1.13	1.18	0.94	0.93	0.64*	0.59†
TAG 52:6-FA14:0	1.23	1.32	0.97	0.97	0.59*	0.51†
TAG 54:7-FA22:5	1.21	1.32	0.93	0.97	0.66†	0.46*
TAG 56:7-FA22:4	1.03	1.14	0.85	0.99	0.65*	0.59*
MAG (17:0)	1.27	2.46	0.47	0.47	0.85	0.06*
MAG (22:6)	3.12	2.60	0.56	0.72	0.61	0.39†

□ Decreased Trajectory (Fold change <1) ■ Increased Trajectory (Fold change >1)

Color scheme based on a 3-color scale with minimum of 0.22, midpoint 1, and maximum 2.

* $P\leq 0.05$. † $0.05<P<0.10$.

BL, baseline; DAG, diacylglycerol; FA, fatty acid; MAG, monoglyceride; NR, nonresponder; RR, rapid responder; SR, standard responder; TAG, triacylglycerol.

[0083] The changes in acylglycerol levels shown in Fig. 5 and in Table 7 show that, at week 6, both responder groups showed notably lower acylglycerol levels (SR: +2.6%; RR: -26.8%) versus NRs (+10.8%), with significant between-group differences for triacylglycerols (Fig. 6, left-most portion). Reductions in acylglycerols most associated with inflammation (monoacylglycerols and diacylglycerols) were more prominent in RRs (Table 7). Acylglycerol level decreases continued at week 12 in RRs despite drug discontinuation for 8 of 9 patients after

week 6, suggesting enhanced metabolic regulation persisted in this group after drug exposure ended.

TABLE 8

Fold Changes in Long Chain Fatty Acid (LCFA) Levels From Baseline to Weeks 6 and 12

LCFAs	Categories	NR		SR		RR	
	Biochemical Name / Ratio	Wk6/B L	Wk12/B L	Wk6/B L	Wk12/B L	Wk6/B L	Wk12/B L
Saturated FAs	Myristate (14:0)	1.02	1.16	1.02	0.98	0.87	0.88
	Pentadecanoate (15:0)	1.01	1.13	0.94	0.99	0.87	0.87
	Margarate (17:0)	1.02	1.12	0.90	0.97	0.83	0.80
MUFAs	Myristoleate (14:1n5)	1.00	1.16	0.95	0.93	0.82	0.94
	Palmitoleate (16:1n7)	0.94	1.22	0.94	0.97	0.85	0.96
	10-heptadecenoate (17:1n7)	0.98	1.24	0.85	0.90	0.81	0.85
	Oleate/vaccenate (18:1)	1.00	1.13	0.99	1.01	0.89	0.92
	10-nonadecenoate (19:1n9)	0.97	1.05	0.92	0.95	0.85	0.83
	Eicosenoate (20:1)	1.02	1.15	0.96	1.00	0.88	0.94
PUFAs (n-3 and n-6)	Tetradecadienoate (14:2)	0.99	1.04	1.03	1.04	0.82	0.73
	Stearidonate (18:4n3)	1.34	1.21	1.16	0.94	0.77	0.63
	Eicosapentaenoate (EPA; 20:5n3)	0.98	1.20	1.01	1.03	0.70	0.22
	Docosapentaenoate (n3 DPA; 22:5n3)	0.89	1.10	0.90	0.95	0.77	0.36
	Docosahexaenoate (DHA; 22:6n3)	0.89	0.98	0.85	0.88	0.77	0.68
	Docosatrienoate (22:3n3)	0.95	1.22	0.73	0.91	0.85	0.67
	Hexadecadienoate (16:2n6)	1.03	1.15	0.98	1.00	0.83	0.87
	Linoleate (18:2n6)	1.08	1.20	0.96	1.01	0.85	0.94
	Linolenate [alpha or gamma; (18:3n3 or 6)]	1.26	1.31	0.99	0.96	0.81	0.94
	Dihomo-linoleate (20:2n6)	1.01	1.13	0.90	0.97	0.85	0.83
	Arachidonate (20:4n6)	0.97	1.10	0.86	0.95	0.84	0.72
	Adrenate (22:4n6)	0.84	1.11	0.83	0.89	0.84	0.75
	Docosapentaenoate (n6 DPA; 22:5n6)	0.94	1.00	0.91	0.95	0.86	0.86
	Docosadienoate (22:2n6)	0.99	1.02	0.91	1.00	0.93	0.89
	Mead acid (20:3n9)	1.05	1.12	1.28	1.26	0.76	0.59†

□ Decreased Trajectory (Fold change <1)

■ Increased Trajectory (Fold change >1)

Color scheme based on a 3-color scale with minimum of 0.22, midpoint 1, and maximum 1.34.

†0.05<P<0.10. BL, baseline; FA, fatty acid; LCFA, long-chain FA; MUFA, monounsaturated FA; NR, nonresponder; PUFA, polyunsaturated FA; RR, rapid responder; SR, standard responder.

[0084] The changes in fatty acid (FA) levels shown in Fig. 6 and in Table 8 show that most long-chain fatty acids (LCFAs), including polyunsaturated FAs (PUFAs) omega-3 and -6, were reduced (fold change <1) at week 6 and week 12 vs baseline in responders regardless of ALT elevation but were elevated (fold change >1) in NRs. Significant reductions were observed at week 6 for SRs (-5.3%; $P<0.01$) and RRs (-16.6%; $P<0.0001$) but not NRs (+0.6%) versus their respective baselines. Decreases in LCFAs and PUFAs may suggest improved FA oxidation in responders, which would be expected to reduce circulating FFAs.

TABLE 9

Fold Changes in Acylcarnitine and 3-hydroxy FA Levels From Baseline to Weeks 6 and 12

Acylcarnitine / 3-hydroxy FA	Categories	NR		SR		RR	
	Biochemical Name / Ratio	Wk6/BL	Wk12/BL	Wk6/BL	Wk12/BL	Wk6/BL	Wk12/BL
Short Chain	Acetylcarnitine (C2)	0.90†	0.98	1.00	0.93	0.92	0.99
Medium Chain	Hexanoylcarnitine (C6)	0.90	1.03	1.00	0.95	0.87	0.99
	Octanoylcarnitine (C8)	1.03	1.09	1.01	1.01	0.81	0.84
	Nonanoylcarnitine (C9)	0.96	0.96	1.03	1.01	0.82	0.79†
	Laurylcarnitine (C12)	1.00	1.05	1.11	1.03	1.00	0.87
Long Chain Saturated	Myristoylcarnitine (C14)	0.93	0.99	1.05	1.02	1.01	0.91
	Palmitoylcarnitine (C16)	0.94	0.99	1.07	1.02	0.97	0.88
	Margaroylcarnitine (C17)	0.90	0.99	0.98	0.93	0.92	0.89
	Stearoylcarnitine (C18)	0.93	0.89	1.00	0.94	0.97	0.86†
	Arachidoylcarnitine (C20)	1.00	1.00	1.00	1.01	0.89	0.90
	Behenoylcarnitine (C22)	1.09	0.96	0.85	0.87	1.09	0.90
	Lignoceroylcarnitine (C24)	0.96	0.93	0.88	1.00	1.07	1.03
	Cerotoylcarnitine (C26)	1.01	1.05	1.07	1.03	1.06	1.04
3-hydroxy metabolism	3-hydroxyhexanoate	1.04	0.92	0.86	0.91	0.91	0.93
	3-hydroxyoctanoate	1.61	1.07	0.78	0.78	0.83	1.14
	3-hydroxydecanoate	1.54	1.01	0.88	0.81	0.84	0.97
	3-hydroxysebacate	1.58	1.00	0.64	0.82	0.92	1.12
	3-hydroxylaurate	1.09	0.93	1.00	0.90	0.86	0.80
	3-hydroxymyristate	0.98	0.89	1.00	0.95	0.88	0.81

	3-hydroxystearate	1.02	0.82	0.84	0.84	0.86	0.83
	3-hydroxyoleate	0.75*	0.83	0.82	1.20	1.12	0.73†

□ Decreased Trajectory (Fold change <1) ■ Increased Trajectory (Fold change >1)

Color scheme based on a 3-color scale with minimum of 0.22, midpoint 1, and maximum 1.34
 * $P \leq 0.05$. † $0.05 < P < 0.10$. BL, baseline; FA, fatty acid; NR, nonresponder; RR, rapid responder; SR, standard responder.

[0085] The results of these studies with regard to fatty acid beta-oxidation ((FA β O) levels are shown in Fig. 7 and in Table 9. Many short- to medium-chain acylcarnitine species were reduced (fold change <1) in RRs vs increased in NRs (fold change >1) (Table 9). Lower levels can reflect improved utilization by the mitochondria at the tissue level 3-hydroxy FA species were significantly reduced for RRs at week 6 vs NRs ($P \leq 0.05$), pointing to improved liver FA oxidation (Figure 7, second portion from the right).

TABLE 10 Fold Changes in Bile Acid Levels From Baseline to Weeks 6 and 12

Bile Acid	Categories Biochemical Name / Ratio	NR		SR		RR		Wk 6		
		Wk6/B L	Wk12/B L	Wk6/B L	Wk12/B L	Wk6/B L	Wk12/B L	SR/N R	RR/N R	RR/S R
Primary	cholate	0.57	0.47	1.14	1.49	0.39	1.93	2.19	2.63	1.20
	glycocholate	1.34	1.51	1.11	0.88	1.55	1.36	2.35	4.09*	1.57
	taurocholate	1.24	1.44	1.39	1.05	1.83	0.75	1.95	4.21*	2.16
	chenodeoxycholic acid sulfate	1.09	0.96	1.66*	1.39	0.68	1.27	1.10	0.86	0.78
	glycochenodeoxycholate	1.22	1.43	1.25	1.23	0.96	0.93	2.42	2.77*	1.15
	taurochenodeoxycholate	1.16	1.35	1.59	1.28	1.12	0.95	2.38	3.35*	1.40
	cholic acid glucuronide	1.50	0.70	1.51	0.98	0.86	1.82	1.10	1.25	1.13
	glycochenodeoxycholate glucuronide	1.18	0.92	0.92	0.92	1.49	0.85	1.23	1.81†	1.48
	glycochenodeoxycholate 3-sulfate	1.21	1.49	0.86†	0.93	1.87	1.44	1.62	4.80*	2.97*
2ndry	deoxycholate	1.10	0.84	0.97	1.13	0.59*	0.87	0.99	1.21	1.21
	deoxycholic acid glucuronide	1.06	0.88	1.30	0.96	0.82	1.26	1.31	1.52	1.16
	glycodeoxycholate	1.06	0.87	1.43	1.52*	1.05	0.84	1.34	2.25†	1.67
	taurodeoxycholate	1.00	0.81	1.73	1.55†	0.99	0.84	0.97	1.69	1.75†
	taurodeoxycholic acid 3-sulfate	0.81	0.71	1.34	1.24	1.78*	0.63	1.61	2.65*	1.64*
	lithocholic acid sulfate	1.36	1.23	0.93	1.46	1.94	2.67	1.04	4.06	3.90
	glycolithocholate sulfate	1.06	0.93	0.79	0.93	1.89	1.04	1.22	2.25	1.84†
	ursodeoxycholate	0.84	0.86	1.62	2.34	0.35*	0.62†	1.26	0.75	0.60
	glycoursodeoxycholate	1.46	1.43	1.40	1.16	0.61*	0.56†	2.30	1.72	0.75
	glycoursodeoxycholic acid sulfate	1.04	0.99	0.95	1.07	1.35	0.58*	1.50	3.80*	2.54*
	tauroursodeoxycholate	0.92	1.00	1.92	1.16	0.66	0.53	3.39	3.04	0.85

tauroursodeoxycholic acid sulfate	1.06	0.98	1.10	1.10	2.07*	0.61	1.58	0.85*	4.20*
hyocholate (gamma-muricholate)	1.10	0.98	1.13	0.97	1.11	1.45	0.89	1.50	1.69
glycochenate sulfate	0.97	1.03	0.94	0.92	1.43*	0.88	1.14	2.09	1.84
taurochenate sulfate	0.84	0.99	1.06	1.08	1.55†	0.69	1.26	2.13*	1.70*
3beta-hydroxy-5-choleonoate	0.96	1.05	1.07	1.07	1.24	0.87	0.73†	1.03	1.41†
glycodeoxycholate 3-sulfate	0.98	0.88	1.01	1.25	1.79†	0.77	1.47	3.39*	2.30*
taurochenodeoxycholic acid 3-sulfate	1.19	1.38	1.09	1.23	2.43†	1.21	1.65	3.44*	3.31*

□ Decreased Trajectory (Fold change <1) ▨ Increased Trajectory (Fold change >1)

Color scheme based on a 3-color scale with minimum of 0.35, midpoint 1, and maximum 6.65.

* $P \leq 0.05$. † $0.05 < P < 0.10$ NR, nonresponder; RR, rapid responder; SR, standard responder.

[0086] The results of these studies with regard to bile acid levels are shown in Fig. 8 and in Table 10. At baseline, about 70% of the analyzed primary and secondary bile acids showed elevated levels in RRs compared with SRs and NRs. For the SR and RR within-group comparisons, most primary bile acid species did not change significantly from baseline to weeks 6 or 12. For RRs, numerous secondary bile acid species were significantly shifted bidirectionally (either upwardly or downwardly) from baseline. At week 6, RRs had increasing trajectories (several significant) vs NRs for numerous primary and secondary bile acid species. SRs trended toward increased bile acid species vs NRs. In SRs, most primary bile acids decreased by ~19% from week 6 to week 12.

[0087] The observed declines in intermediate lipid species suggest that responders (patients with $\geq 30\%$ reduction from baseline in LFC following miricorilant treatment), particularly those with rapid LFC clearance accompanied by efficacy-associated ALT elevations (rapid responders [RR]), experienced enhanced metabolic clearance of lipids and FAs. In RRs, metabolic clearance of acylglycerols continued to improve at week 12 despite discontinuation or interruption of miricorilant after week 6. Rapid changes in liver metabolism, such as increased FA oxidation, can cause transient hepatic stress. This stress may produce a short-term rise in ALT levels as the liver adjusts to the new metabolic conditions. Although this may cause transient hepatic stress, it points to improved hepatic lipid metabolism. Changes in bile metabolism could suggest elevated liver capacity to synthesize bile acids, enhancing lipid emulsification or clearance. The ongoing phase 2b MONARCH study is assessing 100 mg miricorilant twice weekly, a dose that resulted

in improved LFC without ALT elevations in miricorilant's phase 1b study, and a higher dose of 200 mg twice weekly after a 6-week lead-in of 100 mg twice weekly.

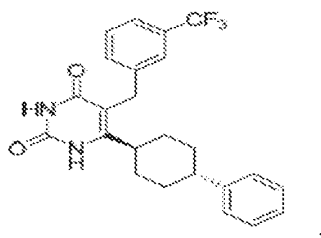
[0088] This study highlights the potential of miricorilant as a MASH treatment and suggests that patients who respond to miricorilant, especially those with rapid LFC reduction and efficacy-associated rise in ALT (RRs), had a significant enhancement in metabolic clearance of FAs. The changes may indicate an increase in cellular FA beta-oxidation, which, despite contributing to transient hepatic stress in some patients, signals improved metabolic regulation and liver health.

[0089] All patents, patent publications, publications, and patent applications cited in this specification are hereby incorporated by reference herein in their entireties as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. In addition, although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

WE CLAIM:

1. A method of treating a fatty liver disease in a patient suffering from, and in need of treatment for, a fatty liver disease,

Wherein said patient is a miricorilant responder patient suffering from an abnormally high baseline liver fat content who has responded to miricorilant administration with a reduction in liver fat content of at least 30% as compared to baseline liver fat content, wherein miricorilant is (E)-6-(4-Phenylcyclohexyl)-5-(3-trifluoromethylbenzyl)-1H-pyrimidine-2,4-dione (“miricorilant”), which has the structure:



the method comprising:

Administering, to said miricorilant responder patient, a further dose of miricorilant,

Said treatment being effective to:

enhance metabolic clearance of fatty acids in said patient, and to provide rapid loss of liver fat content in said patient; or

reduce plasma levels of long-chain fatty acids in said patient, and to reduce polyunsaturated fatty acids in the plasma of the patient by at least about 5 % to about 17 % as compared to baseline levels of polyunsaturated fatty acids, wherein said baseline levels of polyunsaturated fatty acids are determined prior to administration of miricorilant; or

reduce levels of acylglycerols in the plasma of said patient by about 25 % as compared to baseline levels of acylglycerols, wherein said baseline acylglycerol levels are determined prior to administration of miricorilant; or

increase the level of secondary bile acids in the plasma of the patient by about 35 % as compared to the baseline plasma secondary bile acid level, wherein said baseline plasma secondary bile acid level is determined prior to administration of miricorilant;

Whereby:

metabolic clearance of fatty acids in the miricorilant responder patient is enhanced; or
the plasma level of long-chain fatty acids of the miricorilant responder patient is reduced; or
the plasma level of acylglycerols of the miricorilant responder patient is reduced; or
the plasma level of secondary bile acids of the miricorilant responder patient is increased.

2. The method of claim 1, wherein said responder patient responded to miricorilant administration with an increase in alanine aminotransferase (ALT) levels to at least three times the upper limit of normal (ULN) levels of ALT, and said rapid loss of liver fat content was twice as fast as the liver fat content loss observed in responder patients whose ALT levels did not increase to at least three times the ULN levels of ALT.

3. The method of claim 1, wherein said enhanced metabolic clearance of fatty acids comprises enhanced metabolic clearance of long-chain polyunsaturated fatty acids selected from omega-3 polyunsaturated fatty acids and omega-6 polyunsaturated fatty acids.

4. The method of claim 1, wherein said of reduced plasma level of acylglycerols comprises reduced plasma level of triacylglycerols.

5. The method of claim 1, wherein said increased plasma level of secondary bile acids comprises an increased plasma level of a secondary bile acid selected from lithocholate sulfate, taurochenodeoxycholic acid 3-sulfate, and tauroursodeoxycholic acid sulfate.

6. The method of claim 1, wherein said administration of miricorilant is oral miricorilant administration or said use of miricorilant is oral use.

7. The method of claim 1, wherein said miricorilant administration is once daily miricorilant administration or said miricorilant use is once daily miricorilant use.

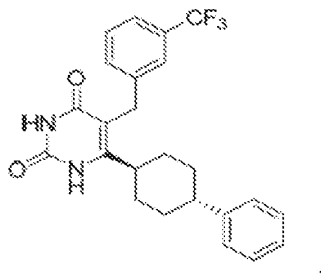
8. The method of claim 1, wherein said further dose of miricorilant is a dose of between about 10 milligrams (mg) and about 1000 mg,

9. The method of claim 1, wherein said effective dose of miricorilant is a dose selected from 50 mg, 100 mg, 125 mg, 150 mg, 200 mg, 300 mg, 400 mg, 500 mg, and 600 mg, or said amount of miricorilant is an amount selected from 50 mg, 100 mg, 125 mg, 150 mg, 200 mg, 300 mg, 400 mg, 500 mg, and 600 mg.

10. The method of claim 1, wherein said administration of miricorilant comprises at least six weeks of miricorilant administration for the treatment of said fatty liver disease.

11. The use of miricorilant for treating a fatty liver disease in a patient suffering from, and in need of treatment for, a fatty liver disease,

Wherein said patient is a miricorilant responder patient suffering from an abnormally high baseline liver fat content who has responded to miricorilant administration with a reduction in liver fat content of at least 30% as compared to baseline liver fat content, wherein miricorilant is (E)-6-(4-Phenylcyclohexyl)-5-(3-trifluoromethylbenzyl)-1H-pyrimidine-2,4-dione (“miricorilant”), which has the structure:



the use comprising:

Said use being effective to:

enhance metabolic clearance of fatty acids in said patient, and to provide rapid loss of liver fat content in said patient, where said rapid loss of liver fat content is a loss of liver fat content over six weeks of said miricorilant administration that is twice as fast as the liver fat content loss observed in responder patients whose ALT levels did not increase to at least three times the upper limit of normal levels of ALT; or

reduce plasma levels of long-chain fatty acids in said patient, and to reduce polyunsaturated fatty acids in the plasma of the patient by at least about 5 % to about 17 % as

compared to baseline levels of polyunsaturated fatty acids, wherein said baseline levels of polyunsaturated fatty acids are determined prior to administration of miricorilant; or

reduce levels of acylglycerols in the plasma of said patient by about 25 % as compared to baseline levels of acylglycerols, wherein said baseline acylglycerol levels are determined prior to administration of miricorilant; or

increase the level of secondary bile acids in the plasma of the patient by about 35 % as compared to the baseline plasma secondary bile acid level, wherein said baseline plasma secondary bile acid level is determined prior to administration of miricorilant.

12. The use of claim 11, wherein said responder patient responded to miricorilant administration with an increase in alanine aminotransferase (ALT) levels to at least three times the upper limit of normal (ULN) levels of ALT, and said rapid loss of liver fat content was twice as fast as the liver fat content loss observed in responder patients whose ALT levels did not increase to at least three times the ULN levels of ALT.

13. The use of claim 11, wherein said enhanced metabolic clearance of fatty acids comprises enhanced metabolic clearance of long-chain polyunsaturated fatty acids selected from omega-3 polyunsaturated fatty acids and omega-6 polyunsaturated fatty acids.

14. The use of claim 11, wherein said of reduced plasma level of acylglycerols comprises reduced plasma level of triacylglycerols.

15. The use of claim 11, wherein said increased plasma level of secondary bile acids comprises an increased plasma level of a secondary bile acid selected from lithocholate sulfate, taurochenodeoxycholic acid 3-sulfate, and tauroursodeoxycholic acid sulfate.

16. The use of claim 11, wherein said administration of miricorilant is oral miricorilant administration or said use of miricorilant is oral use.

17. The use of claim 11, wherein said miricorilant administration is once daily miricorilant administration or said miricorilant use is once daily miricorilant use.

18. The use of claim 11, wherein said use comprises use of between about 10 milligrams (mg) and about 1000 mg miricorilant in the treatment of said fatty liver disease.

19. The use of claim 11, wherein said effective dose of miricorilant is a dose selected from 50 mg, 100 mg, 125 mg, 150 mg, 200 mg, 300 mg, 400 mg, 500 mg, and 600 mg, or said amount of miricorilant is an amount selected from 50 mg, 100 mg, 125 mg, 150 mg, 200 mg, 300 mg, 400 mg, 500 mg, and 600 mg.

20. The use of claim 11, wherein said use comprises use of miricorilant for at least six weeks for the treatment of said fatty liver disease.