

CONCOMITANT ADMINISTRATION OF MIRICORILANT WITH CYP2C19 INHIBITORS

BACKGROUND

[0001] Concomitant administration of two drugs, resulting in the simultaneous presence of the two drugs in a subject, may alter the effects of one or the other, or both, of these drugs. Such concomitant administration may lead to adverse effects since the metabolism and/or elimination of each drug may reduce or interfere with the metabolism and/or elimination of the other drug(s), thus altering the blood levels of those drugs as compared to the blood levels of those drugs when administered alone. Such alterations of drug effects are termed drug-drug interactions (DDIs). Concomitant administration of different drugs may increase the risk of unintended and possibly deleterious effects of one or both of two co-administered drugs.

[0002] For example, the required dose of a drug is often strongly affected by the amount and rate of its degradation in, and elimination from, the body (e.g., by liver or kidney action). However, the presence of a second drug in the body, which is also being acted upon, e.g., by the liver or kidney, can have significant effects on the amount and rate of degradation of the first drug, and can increase or decrease the amount of the first drug that remains in the body at a given time as compared to the amount that would have been present at that time in the absence of the second drug. Thus, for example, the presence of a second drug that is an inhibitor of an enzyme that metabolizes a first drug will inhibit the metabolism of the first drug and thus can often increase the plasma levels of that first drug as compared to the plasma levels resulting from the same dose of the first drug administered in the absence of the second drug. Such enzyme inhibition results in an increase in the effective dose of the first drug as compared to its administration without the second drug. If the first drug has toxic side effects, such an increase in effective dose of the first drug may lead to dangerous toxicity that would not have been expected were the second drug not present.

[0003] Cytochrome P450 (abbreviated as CYP or P450) enzymes are hemoproteins of approximately 500 amino acids. Fifty-seven human functional CYP genes have been identified. The human CYP genes are classified into 18 families and 44 subfamilies designated by a capital letter. Classification is based on the amino acid sequence identity of the encoded proteins (Nelson, 2009). Eleven enzymes from CYP families 1, 2 and 3 (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP3A5) primarily contribute to drug and chemical metabolism

(Rendic et al., *Chem Res Tox* 28:38-42 (2015); Rendic et al., *Arch Toxicol* 95(2):395-472 (2021)). These enzymes contribute to the biotransformation of approximately 70% of clinically used drugs. Generally, these enzymes provide a clearance mechanism for drugs, toxins, and other molecules an animal may encounter, and facilitate elimination of such molecules from the body in urine and/or bile. The individual CYP enzymes exhibit distinct, but sometimes overlapping, substrate and inhibitor selectivities.

[0004] For example, many therapeutically important drugs are metabolized by the CYP2C19 enzyme. The U.S. Food and Drug Administration (FDA) lists lansoprazole and omeprazole as “sensitive index substrates” of the cytochrome P450 enzyme CYP2C19. Sensitive index substrates are index drugs that demonstrate an increase in AUC of ≥ 5 -fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies (see “Drug Development and Drug Interactions | Table of Substrates, Inhibitors and Inducers” at the FDA website (www.fda.gov) page “/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table2-1” (as accessed in January 2025). Other CYP2C19 substrate drugs include, e.g., amiodarone, amitriptyline, diazepam, esomeprazole, fluconazole, fluoxetine, fluvoxamine, glimepiride, glimepiride, ketoconazole, lapatinib, naftodipil, pantoprazole, ticlopidine, tipifarnib, tranylcypromine, voriconazole, atomoxetine, brivaracetam, carisoprodol, chloramphenicol, citalopram, clobazam, clomipramine, clopidogrel, cyclophosphamide, doxepin, escitalopram, flibanserin, hexobarbital, imipramine, labetalol, mavacamten, moclobemide, nelfinavir, nilutamide, ospemifene, phenobarbital, phenytoin, pomalidomide, primidone, progesterone, proguanil, propranolol, r-mephobarbital, r-warfarin, s-mephenytoin, teniposide, tofacitinib, venlafaxine, and vilazodone (see, e.g., Backman et al., *Pharmacol Rev* 68:168-241 (2016); De Jong et al., *Front Pharmacol.* 2023; 14: 1201906; Edinoff et al. *Health Psychol Res.* 2022; 10(4): 39576; and the U.S. Food and Drug Administration (FDA) web page “drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers” and the Drug Interactions Flockhart Table™, accessible at the web-site “drug-interactions.medicine.iu.edu/MainTable.aspx”).

[0005] Many drugs inhibit the activity of one or more CYP enzymes, and thus have the potential to cause a drug-drug interaction. Thus, a therapeutic dose of a first drug that is metabolized by a CYP enzyme may become a toxic dose when the first drug is administered with a second drug that inhibits that same CYP enzyme, since the CYP enzyme activity regarding the first drug will be reduced by the presence of the second drug, leading to

increased levels of the first drug (as compared to the levels obtained by the same dose of the first drug in the absence of the second drug). In this way, the activity of many enzymes may be inhibited by clinically important drugs. Such inhibition may affect the metabolism, and so the blood levels, of those drugs and of other drugs which may also be present in a patient receiving such enzyme-inhibiting drugs.

[0006] The FDA lists fluvoxamine (Prozac[®], a selective serotonin reuptake inhibitor) as a strong inhibitor of CYP2C19, and lists N-3-benzyl-nirvanol, loratadine, nootkatone, and ticlopidine as *in vitro* selective inhibitors of CYP2C19. A longer list of CYP2C19 inhibitors includes fluvoxamine, N-3-benzyl-nirvanol, loratadine, nootkatone, ticlopidine, armodafinil, chloramphenicol, cimetidine, citalopram, esomeprazole, felbamate, fluconazole, fluoxetine, isoniazid, ketoconazole, luliconazole, modafinil, omeprazole, oritavancin, quercetin, rucaparib, ticlopidine, topiramate, and many oral contraceptives, and voriconazole (see the U.S. Food and Drug Administration (FDA) web page “drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers” and the Drug Interactions Flockhart Table[™], accessible at the web-site “drug-interactions.medicine.iu.edu/MainTable.aspx”). Clinically useful drugs that are also strong inhibitors of the metabolic enzyme CYP2C19 include: armodafinil, chloramphenicol, cimetidine, citalopram, esomeprazole, felbamate, fluconazole, fluoxetine, isoniazid, ketoconazole, luliconazole, modafinil, omeprazole, oritavancin, quercetin, rucaparib, ticlopidine, topiramate, and many oral contraceptives.

[0007] 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 name for miricorilant is “CORT118335”.

SUMMARY

[0008] Applicant discloses herein that miricorilant was hepatically eliminated, primarily by CYP2C19 (94%) with only very minor contributions by CYP1A2, 2C8, 2C9, 2D6 (1% each) and 3A4 (2%). Since miricorilant is subject to significant metabolism by CYP2C19,

concomitant administration of a standard dose of miricorilant with a strong CYP2C19 inhibitor such as fluvoxamine would be expected to cause a significant (e.g., greater than 5-fold) increase in miricorilant plasma levels as compared to the miricorilant plasma levels resulting from the standard dose of miricorilant in the absence of the strong CYP2C19 inhibitor. Thus, it would be expected that concomitant administration of miricorilant with a strong CYP2C19 inhibitor would lead to excessive plasma levels of miricorilant, which might be unsafe, and that, significant reductions in miricorilant dosages would be required when miricorilant was administered in combination with a strong CYP2C19 inhibitor.

[0009] Surprisingly, Applicant determined that it would be safe to co-administer miricorilant and a strong CYP2C19 inhibitor to human subjects without modifying the miricorilant dose. Applicant discloses herein that miricorilant may be concomitantly administered with a CYP2C19 inhibitor, including with a strong CYP2C19 inhibitor, without reduction in the miricorilant dose. Such concomitant administration of a CYP2C19 inhibitor and miricorilant is believed to be safe for the subject and to provide the therapeutic benefits of both drugs to the subject.

[0010] Accordingly, Applicant discloses herein that unmodified doses of miricorilant may be safely administered along with CYP2C19 inhibitors, including strong CYP2C19 inhibitors. Thus, doses of miricorilant need not be adjusted when miricorilant is administered concomitantly with a CYP2C19 inhibitor such as, e.g., fluvoxamine, N-3-benzyl-nirvanol, loratadine, nootkatone, ticlopidine, armodafinil, chloramphenicol, cimetidine, citalopram, esomeprazole, felbamate, fluconazole, fluoxetine, isoniazid, ketoconazole, luliconazole, modafinil, omeprazole, oritavancin, quercetin, rucaparib, ticlopidine, topiramate, voriconazole, or an oral contraceptive. In embodiments, doses of miricorilant need not be adjusted when miricorilant is administered concomitantly with a strong CYP2C19 inhibitor such as, e.g., fluvoxamine, N-3-benzyl-nirvanol, loratadine, nootkatone, or ticlopidine.

[0011] Applicant discloses herein that concomitant administration of miricorilant with a strong CYP2C19 inhibitor is safe. Surprisingly, administration of miricorilant along with a strong CYP2C19 inhibitor does not require miricorilant dose adjustment. The methods disclosed herein surprisingly provide safe methods for administering drug combinations that were previously expected to be unsafe, allowing concomitant administration of drug combinations with miricorilant. Such drug combinations are believed to provide more effective treatments than treatment with only one of the drugs in the absence of the other. The

surprising ability to safely administer these drug combinations provides advantages including more effective treatments, absence of previously expected side effects, and other advantages.

[0012] 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.

[0013] Accordingly, Applicant discloses herein that administration of miricorilant along with inhibitors of CYP2C19 is safe, and that administration of miricorilant provides improved methods of treating patients suffering from fatty liver diseases.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] Fig. 1A shows the concentration of miricorilant in plasma over time following administration of 600 milligrams (mg) miricorilant alone to healthy subjects on Day 1 of the study (these subjects had not received fluvoxamine).

[0015] Fig. 1B shows the concentration of miricorilant in plasma over time following administration of 600 mg miricorilant in the presence of once daily 50 mg fluvoxamine on Day 10 of the study (these subjects had received 50 mg fluvoxamine once daily for 10 days).

[0016] Fig. 1C 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.

[0017] Fig. 2 shows the mean concentration of miricorilant in plasma over time in the absence of (triangles) and the presence of (squares) 50 milligrams (mg) per day (QD) fluvoxamine. Fluvoxamine is a strong inhibitor of the metabolic enzyme CYP2C19. Although miricorilant plasma exposure (C_{max} , $AUC_{(0-last)}$, $AUC_{(0-inf)}$) was somewhat higher in presence of fluvoxamine as compared to the plasma exposure when miricorilant was administered alone; surprisingly, however, this increase was not as high as expected – much less than 5-fold – so that no miricorilant dose reduction would be required in the presence of fluvoxamine.

[0018] Fig. 3 shows plasma concentrations of [¹⁴C]-miricorilant and total radioactivity over time following a single oral dose of [¹⁴C]-miricorilant 150 mg (administered fed) in male healthy volunteers (30—65 years; BMI 18—30 kg/m²).

DETAILED DESCRIPTION

[0019] Miricorilant is a mixed agonist/antagonist of the glucocorticoid receptor and an antagonist of the mineralocorticoid receptor that is primarily metabolized by the cytochrome P450 enzyme CYP2C19. Thus, miricorilant is a CYP2C19 substrate. Strong inhibitors of CYP2C19 are, by definition, those molecules that cause a 5-fold or greater increase in plasma levels of CYP2C19 substrates when co-administered with those substrates. Surprisingly, administration of miricorilant along with a strong CYP2C19 inhibitor led to much less than 5-fold increase in plasma miricorilant levels. Thus, despite its metabolic degradation by CYP2C19, Applicant has discovered that concomitant administration of miricorilant with a strong CYP2C19 inhibitor does not increase miricorilant plasma levels above that observed for miricorilant alone to the extent that would require miricorilant dose adjustment when miricorilant is administered to a patient who is also receiving a strong CYP2C19 inhibitor. Thus, concomitant administration of miricorilant with a strong CYP2C19 inhibitor is safe. Surprisingly, adjustment of the miricorilant dose is not required when miricorilant is administered along with a strong CYP2C19 inhibitor.

[0020] Thus, Applicant discloses herein the surprising methods for concomitant administration of miricorilant with CYP2C19 inhibitors in which the dose of miricorilant is unchanged, or not greatly reduced, as compared to the miricorilant dose for administration in the absence of the CYP2C19 inhibitor. In embodiments, the CYP2C19 inhibitor is a strong CYP2C19 inhibitor, which may be, e.g., fluvoxamine, N-3-benzyl-nirvanol, loratadine, nootkatone, ticlopidine, or other strong CYP2C19 inhibitor. In embodiments, the CYP2C19 inhibitor is a CYP2C19 inhibitor selected from fluvoxamine, N-3-benzyl-nirvanol, loratadine, nootkatone, ticlopidine, armodafinil, chloramphenicol, cimetidine, citalopram, esomeprazole, felbamate, fluconazole, fluoxetine, isoniazid, ketoconazole, luliconazole, modafinil, omeprazole, oritavancin, quercetin, rucaparib, ticlopidine, topiramate, voriconazole, and an oral contraceptive.

[0021] As discussed in more detail in Example 1, Applicant discloses herein that miricorilant is a substrate of the cytochrome P450 enzyme CYP2C19. In vitro studies with human CYP metabolizing enzymes indicated that miricorilant was hepatically eliminated, primarily by

CYP2C19 (94%) with only very minor contributions by CYP1A2, 2C8, 2C9, 2D6 (1% each) and 3A4 (2%). These results suggest that concomitant administration of miricorilant with a strong CYP2C19 inhibitor, such as fluvoxamine (or another strong CYP2C19 inhibitor, such as, e.g., N-3-benzyl-nirvanol, loratadine, nootkatone, or ticlopidine) should greatly increase (i.e., by 5-fold or more) exposure to miricorilant administered to a subject.

[0022] Applicant discloses herein the surprising discovery that miricorilant may be safely co-administered with CYP2C19 inhibitor drugs without need for reducing the dosage of miricorilant below that of the miricorilant dosage for administration in the absence of a CYP2C19 inhibitor. For example, miricorilant and a CYP2C19 inhibitor may be co-administered to treat antipsychotic-induced weight gain (AIWG), a fatty liver disease such as nonalcoholic steatohepatitis (NASH), and fatty liver disease co-morbidities such as Type 2 diabetes, obesity, and dyslipidemia, without need for reducing the dosage of miricorilant. CYP2C19 inhibitors that may be safely co-administered with miricorilant include, e.g., fluvoxamine, N-3-benzyl-nirvanol, loratadine, nootkatone, ticlopidine, armodafinil, chloramphenicol, cimetidine, citalopram, esomeprazole, felbamate, fluconazole, fluoxetine, isoniazid, ketoconazole, luliconazole, modafinil, omeprazole, oritavancin, quercetin, rucaparib, ticlopidine, topiramate, voriconazole, and many oral contraceptives.

[0023] Miricorilant and a CYP2C19 inhibitor may be co-administered to treat metabolic disorders (e.g., fatty liver diseases and AIWG) without need for reducing the dosage of miricorilant. Miricorilant and a CYP2C19 inhibitor may be co-administered to treat AIWG without need for reducing the dosage of miricorilant. Miricorilant and a CYP2C19 inhibitor may be co-administered to treat fatty liver diseases, or AIWG without need for reducing the dosage of miricorilant. Such co-administration of miricorilant and a CYP2C19 inhibitor provides therapeutically effective levels of both miricorilant and of the CYP2C19 inhibitor at the same time in the patient. CYP2C19 inhibitors that may be safely co-administered with miricorilant without need for reducing the dosage of miricorilant include, e.g., fluvoxamine, N-3-benzyl-nirvanol, loratadine, nootkatone, ticlopidine, armodafinil, chloramphenicol, cimetidine, citalopram, esomeprazole, felbamate, fluconazole, fluoxetine, isoniazid, ketoconazole, luliconazole, modafinil, omeprazole, oritavancin, quercetin, rucaparib, ticlopidine, topiramate, voriconazole, and many oral contraceptives.

[0024] In embodiments, Applicant discloses a method of treating a disorder, said treatment comprising administration of miricorilant, said miricorilant having a single agent dose that is an amount of miricorilant that is effective to treat said disorder when miricorilant is the only

agent administered for said treatment, the method comprising administering to a patient in need of treatment for said disorder:

a) an effective dose of a therapeutic agent, wherein said therapeutic agent is an inhibitor of CYP2C19 enzyme metabolism; and

b) an effective dose of miricorilant, wherein said miricorilant effective dose is substantially the same as said miricorilant single agent dose;

Wherein a) and b) are performed at times effective to provide the patient with an effective level of miricorilant and an effective level of the therapeutic agent at the same time,

Whereby the disorder is treated.

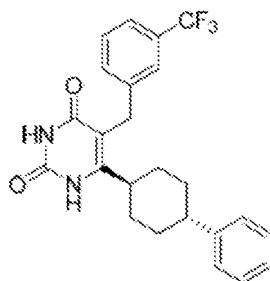
[0025] In embodiments, the therapeutic agent that is an inhibitor of CYP2C19 enzyme metabolism may be fluvoxamine, N-3-benzyl-nirvanol, loratadine, nootkatone, ticlopidine, armodafinil, chloramphenicol, cimetidine, citalopram, esomeprazole, felbamate, fluconazole, fluoxetine, isoniazid, ketoconazole, luliconazole, modafinil, omeprazole, oritavancin, quercetin, rucaparib, ticlopidine, topiramate, voriconazole, or an oral contraceptive. In embodiments, the disorder is antipsychotic-induced weight gain (AIWG) or a fatty liver disease. In embodiments, the disorder is a fatty liver disease (e.g., non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), alcohol related fatty liver disease (AFLD) or other fatty liver disease). In embodiments in which the disorder is a fatty liver disease, the therapeutic agent may be, e.g., semaglutide, resmetirom, or lanifibranor. In embodiments, the disorder is AIWG. In embodiments in which the disorder is AIWG, the antipsychotic therapeutic agent may be, e.g., risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, asenapine, lurasidone, iloperidone, cariprazine, brexpiprazole, or clozapine.

[0026] For example, applicant has surprisingly discovered that miricorilant may be safely administered to subjects concomitantly receiving a CYP2C19 inhibitor without the need to modify the miricorilant dose due to CYP2C19 inhibition. This discovery is surprising, since miricorilant has been shown in *in vitro* studies to be mostly (greater than 90%) metabolized by CYP2C19 in vitro. However, in a clinical study in healthy volunteers designed to assess the propensity for drug-drug interaction with the strong CYP2C19 inhibitor fluvoxamine to increase the exposure to miricorilant, the expected greater than 5-fold increase in miricorilant plasma level was not observed, surprisingly indicating that miricorilant dose modification, with respect to the miricorilant dose to be administered in the absence of CYP2C19

inhibitors, is not required when miricorilant is administered with an inhibitor of CYP2C19 in a clinical setting. Thus, such concomitant administration of miricorilant with a strong CYP2C19 inhibitor is safe.

[0027] Applicant's surprising discovery is believed to apply to patients suffering from a disease or disorder amenable to treatment by miricorilant and receiving a CYP2C19 inhibitor, including a strong CYP2C19 inhibitor. Applicant discloses herein the surprising discovery that patients receiving miricorilant at a therapeutic dose for the treatment of a disorder may safely benefit from concomitant treatment with miricorilant and a CYP2C19 inhibitor, and may continue to receive miricorilant at the same, or substantially the same, therapeutic dose (as was administered when miricorilant was given without the CYP2C19 inhibitor, i.e., the miricorilant single agent dose) while also additionally receiving that CYP2C19 inhibitor. Applicant further discloses herein the surprising discovery that patients receiving a CYP2C19 inhibitor for the treatment of a disorder may benefit from concomitant treatment with that CYP2C19 inhibitor and miricorilant, and may receive miricorilant at its single agent dose, or a dose substantially the same as the miricorilant single agent dose, while also receiving that CYP2C19 inhibitor.

[0028] 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).

[0029] 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.

[0030] 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.

[0031] 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

[0032] 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.

[0033] 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.

[0034] 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.

[0035] 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).

[0036] 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.

[0037] 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.

[0038] As used herein, the term “single agent dose” refers to an effective dose of a drug or pharmaceutical preparation that is administered when that drug or pharmaceutical preparation is administered alone, that is, when that drug or pharmaceutical preparation is administered in the absence of other drugs or pharmaceutical preparations.

[0039] As used herein, the terms “co-administration”, “concomitant administration”, “combined administration”, “combination treatment”, and the like refer to the administration of at least two pharmaceutical agents to a subject to treat a disease or condition. The two agents may be administered simultaneously, or sequentially in any order during the entire or portions of the treatment period. The at least two agents may be administered following the same or different dosing regimens. Such agents may include, for example, *e.g.*, miricorilant

and another drug (which other drug is a CYP2C19 inhibitor), which other drug may be, e.g., a drug useful in treating a fatty liver disease, a drug useful in treating antipsychotic-induced weight gain, or another therapeutic agent. In some cases, one agent is administered following a scheduled regimen while the other agent is administered intermittently. In embodiments, miricorilant is administered intermittently. In some cases, both agents are administered intermittently. In some embodiments, the one pharmaceutical agent may be administered daily, and the other pharmaceutical agent may be administered every two, three, or four days.

[0040] 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.

[0041] "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.

[0042] "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.

[0043] 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.

[0044] 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.

[0045] As used herein, the terms “AUC_{0-tau}” and “AUC_(0-tau)” refer to the AUC from time zero to time tau.

[0046] As used herein, the terms “AUC₀₋₂₄” and “AUC₍₀₋₂₄₎” refer to the AUC from time zero to hour 24 post dose.

[0047] As used herein, the terms “AUC_{0-inf}” and “AUC_(0-inf)” refer to the AUC from time 0 to extrapolated to infinity.

[0048] 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}).

[0049] As used herein, the term “BCRP” refers to breast cancer resistance protein.

[0050] As used herein, the term “BIW” refers to twice per week, as in twice weekly drug administration.

[0051] As used herein, the term “BMI” refers to body mass index.

[0052] As used herein, the term “QD” refers to once daily, as in once daily drug administration.

[0053] As used herein, the term “CI” refers to confidence interval.

[0054] As used herein, the term “C_{last}” refers to the last measurable concentration of the analyte.

[0055] As used herein, the term “C_{max}” refers to the maximum observed plasma concentration of the analyte.

[0056] As used herein, the term “CV” refers to coefficient of variance.

[0057] As used herein, the term “CV%” refers to coefficient of variation expressed as a per cent.

[0058] As used herein, the term “GM” refers to geometric mean.

[0059] As used herein, the term “G-CV%” refers to geometric coefficient of variance (in %).

[0060] As used herein, the term “GMR” refers to adjusted geometric mean ratio.

[0061] 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 ($t_{1/2}$)).

[0062] 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.

[0063] As used herein, an “enzyme substrate” or a “substrate” is a molecule that may be metabolized by an enzyme. For example, clinically useful molecules that are substrates of the cytochrome P450 enzyme CYP2C19 include, but are not limited to, lansoprazole, omeprazole, amiodarone, amitriptyline, diazepam, esomeprazole, fluconazole, fluoxetine, fluvoxamine, glimepiride, glimepiride, ketoconazole, lapatinib, naftodipil, pantoprazole, ticlopidine, tipifarnib, tranilcyproline, voriconazole, atomoxetine, brivaracetam, carisoprodol, chloramphenicol, citalopram, clobazam, clomipramine, clopidogrel, cyclophosphamide, doxepin, escitalopram, flibanserin, hexobarbital, imipramine, labetalol, mavacamten, moclobemide, nelfinavir, nilutamide, ospemifene, phenobarbital, phenytoin, pomalidomide, primidone, progesterone, proguanil, propranolol, r-mephobarbital, r-warfarin, s-mephenytoin, teniposide, tofacitinib, venlafaxine, vilazodone. Further CYP2C19 substrate drugs include, without limitation, drugs useful in treating diabetes (e.g., glimepiride, glimepiride, tolbutamide, and metformin); psychosis, anxiety, and depression (e.g., perphenazine, amitriptyline, venlafaxine, R-tofisopam, and diazepam); cardiac disorders and

hypertension (e.g., amiodarone and naftodipil); cancer (e.g., CPI-613, dabrafenib, IN-1130, lapatinib, and tipifarnib)(see Beckman et al., Pharmacol Rev 68:168-241 (2016)); drugs useful for treating a fatty liver disease; drugs useful for treating antipsychotic-induced weight gain; and other clinically useful drugs.

[0064] As used herein, the terms “enzyme inhibitor” and “inhibitor” (when referring to the action of an enzyme) refer to a molecule that reduces the functional activity of an enzyme. Enzyme inhibition is measured by determining enzyme activity in the presence of the substrate and the inhibitor, and comparing that activity with respect to the enzyme activity in the absence of the inhibitor. For example, a molecule that inhibits or reduces the activity of the metabolic enzyme CYP2C19 is a CYP2C19 inhibitor; CYP2C19 inhibitors include fluvoxamine, N-3-benzyl-nirvanol, loratadine, nootkatone, ticlopidine, armodafinil, chloramphenicol, cimetidine, citalopram, esomeprazole, felbamate, fluconazole, fluoxetine, isoniazid, ketoconazole, luliconazole, modafinil, omeprazole, oritavancin, quercetin, rucaparib, ticlopidine, topiramate, and many oral contraceptives.

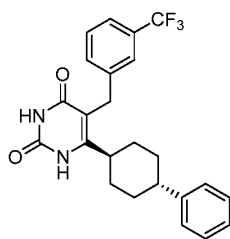
[0065] As used herein, a “strong enzyme inhibitor” or a “strong inhibitor” is an enzyme inhibitor that causes an increase of ≥ 5 -fold in the plasma AUC values or more than 80% decrease in clearance of a sensitive substrate of the enzyme.

[0066] As used herein, a “moderate enzyme inhibitor” and a “moderate inhibitor” is an enzyme inhibitor that causes a ≥ 2 -fold to ≤ 5 -fold increase in the plasma AUC values or 50-80% decrease in clearance of a sensitive substrate of the enzyme.

[0067] As used herein, a “weak enzyme inhibitor” and a “weak inhibitor” is an enzyme inhibitor that causes a ≥ 1.25 -fold but < 2 -fold increase in the plasma AUC values or 20-50% decrease in clearance of a sensitive substrate of the enzyme.

[0068] As used herein, the term “oral contraceptive” refers to a steroid drug, or drug combination, that is administered orally for the prevention of pregnancy. Oral contraceptives typically contain progesterone, or both estrogen and progesterone, or analogs of those steroids. Examples of oral contraceptives include, for example, etonogestrel, levonorgestrel, medroxyprogesterone, ethinyl estradiol, and others.

[0069] 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).

[0070] As used herein, the term “CYP2C19” refers to the cytochrome P450 enzyme subtype 2C19. In humans, the most common form has 490 amino acids, and has the UniProtKB accession number UniProtKB/Swiss-Prot:P33261 (protein P33261.4). The gene encoding human CYP2C19 has Gene ID 1557.

EXAMPLE 1. In vitro CYP phenotyping assay

[0071] In vitro study was carried out to assess the contribution of eight cytochrome P450 (CYP) isoforms, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP3A5, to the metabolism of miricorilant (also termed “CORT118335”). These CYP isoforms heterologously expressed in E. coli were obtained as individual isoforms from Cypex (CYP bacosomes).

[0072] The test compound (final assay concentration 5 μ M, 1% DMSO) or a marker for each isoform (final assay concentration 3 μ M, 1% DMSO) was added to reaction tubes in a 96 well plate format. The markers for each isoform are listed in Table 1 below.

TABLE 1. CYP isoform markers

CYP Isoform	Marker
1A2	Carvediol
2B6	Bupropion
2C8	Montelukast
2C9	Carvediol
2C19	Carvediol
2D6	Carvediol
3A4	Carvediol
3A5	Midazolam

[0073] Individual CYP bacosomes (final assay concentration 100 pmol/mL) were added and the tubes were warmed for 3 minutes whilst mixing on a BioShake IQ (37°C, 1500rpm). NADPH (final assay concentration 1 mM) was added and the reaction was mixed. Aliquots were removed at t = 2, 5, 15, 30, 45 and 60 minutes, added to methanol containing an internal

standard (1 μ M tolbutamide), mixed and placed at -20°C for at least an hour to quench the reaction and allow the protein to precipitate. All samples were centrifuged (2500 x g, 20 minutes, 4°C). The supernatants were transferred to a fresh 96 well plate, compatible with an auto-sampler. The plate was sealed with a pre-slit silicone mat and analysed by LC-MS/MS. Reactions were performed in duplicate at 37°C and in 0.1 M phosphate buffer (pH 7.4).

Data Analysis

[0074] The results were plotted as $\ln(\text{concentration})$ versus time. The elimination rate constant (slope of the regression line, k) was calculated as follows:

$$k = (\ln(0) - \ln C(t)) / t$$

where $C(t)$ is the concentration at time t and $C(0)$ is the starting concentration.

The intrinsic clearance (Cl_{int}), was calculated as follows: $Cl_{int} = [CYP]$

where $[CYP]$ is the CYP concentration in the assay.

Results

[0075] The intrinsic clearance observed for each individual CYP isoform was used to calculate the percentage contribution of each isoform to the metabolism of miricorilant. The results are summarized in Table 2.

TABLE 2. Intrinsic clearance and % contribution for each CYP isoform

	Intrinsic clearance $\mu\text{L}/\text{min}/\text{nmol CYP}$	% Contribution
CYP1A2	44	1
CYP2B6	NTD	NTD
CYP2C8	79	1
CYP2C9	49	1
CYP2C19	6304	94
CYP2D6	66	1
CYP3A4	164	2
CYP3A5	NTD	NTD

NTD = no turnover detected

[0076] As shown above, *in vitro* studies with human CYP metabolizing enzymes indicated that miricorilant was metabolized primarily by CYP2C19 (94%) with only very minor contributions by CYP1A2, 2C8, 2C9, 2D6 (1% each) and 3A4 (2%). Since miricorilant is subject to significant metabolism by CYP2C19, we investigated the effect of CYP2C19 inhibition on the exposure of miricorilant (using a strong index inhibitor).

EXAMPLE 2. Clinical drug-drug interaction study in healthy volunteers

[0077] Applicant discloses herein that metabolic elimination of miricorilant is primarily by CYP2C19. As noted above, since miricorilant is subject to significant metabolism by CYP2C19, co-administration of miricorilant and a CYP2C19 inhibitor to a human subject would be expected to lead to large increases in plasma exposure of the CYP2C19 substrate (miricorilant) as compared to miricorilant plasma exposure in the absence of a CYP2C19 inhibitor.

[0078] The pharmacokinetics (PK) of miricorilant were measured in healthy subjects by administration of single oral doses of miricorilant in the presence and absence of the strong CYP2C19 inhibitor, fluvoxamine. In particular, subjects were administered 50 milligram (mg) doses of fluvoxamine daily on Days 4 – 12, and each subject was administered a single 600 mg dose of miricorilant on Day 1 and on Day 10, of the study. Both drugs were orally administered to fed subjects.

[0079] Repeated once-daily administration of doses of miricorilant in the absence of other compounds were investigated. Fig. 1C 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 3. ($AUC_{(0-24)}$, 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.

[0080] 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).

TABLE 3 Miricorilant Exposure – 150 mg doses of Miricorilant

	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)

[0081] The plasma concentrations of miricorilant over time following administration of 600 mg miricorilant in individual subjects are shown in Fig. 1A and 1B. 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 ($n = 26$).

[0082] Fig. 2 and Table 4 show the concentration of miricorilant (following administration of 600 mg miricorilant) in plasma over time in the absence of (triangles) and the presence of (squares) 50 milligrams (mg) per day (QD) fluvoxamine. Fluvoxamine is a strong inhibitor of the metabolic enzyme CYP2C19, and so administration of fluvoxamine with miricorilant would be expected to cause an increase of ≥ 5 -fold in the plasma AUC values or more than 80% decrease in clearance of miricorilant, a sensitive substrate of the enzyme. Although miricorilant plasma exposure (C_{max} , $AUC_{(0-last)}$, AUC_{0-inf}) was somewhat higher in presence of fluvoxamine as compared to the plasma exposure when miricorilant was administered alone, it was surprisingly much lower than would have been expected (much less than a 5-fold higher).

TABLE 4 MIRICORILANT EXPOSURE (600 mg dose) with and without FLUVOXAMINE

PK Parameter	Miricorilant alone (adjusted geometric mean) (Day 1)	Miricorilant + fluvoxamine (adjusted geometric mean) (Day 10)	Ratio	90% CI Lower	90% CI Upper
AUC_{0-inf} (ng*h/mL)	6700	14600	2.18	1.96	2.42
$AUC_{(0-last)}$ (ng*h/mL)	6140	11700	1.90	1.73	2.09
C_{max} (ng/mL)	492	643	1.31	1.21	1.41

[0083] Miricorilant exposure (as measured by AUC_{0-inf}) in the presence of the strong CYP2C19 inhibitor fluvoxamine was approximately 2-fold higher compared to the miricorilant exposure in the absence of fluvoxamine. The fold increase in exposure is on the lower end of what is considered moderate (range: 2-5-fold). Similarly, the maximum miricorilant plasma concentration following administration was increased by only a small amount by concomitant administration with fluvoxamine. As shown in Table 3 above, the miricorilant C_{max} when administered alone (Day 1) was 492 ng/mL, while miricorilant C_{max}

on Day 10 in the presence of fluvoxamine was 643 ng/mL (i.e., only about 30% higher in the presence of fluvoxamine). These results were surprising, since strong CYP2C19 inhibitors are expected to increase the exposure of concomitantly administered drugs by at least 5-fold. Such large increases were not observed.

[0084] These results indicate that miricorilant may be safely administered with other drugs that inhibit cytochrome P450 enzyme CYP2C19. These results further indicate that the dosage of miricorilant, and the dosages of such other drugs, need not be adjusted when miricorilant is administered along with another drug that inhibits cytochrome P450 enzyme CYP2C19.

[0085] These results were surprising in view of the previously observed *in vitro* metabolism of miricorilant by CYP2C19. Such *in vitro* results would suggest that strong CYP2C19 inhibitors would greatly increase (≥ 5 -fold) miricorilant exposure *in vivo*, and that concomitant administration of miricorilant with a strong CYP2C19 inhibitor would require dose adjustment in order to avoid unsafe excess plasma concentrations of miricorilant. The surprising results of the clinical drug interaction study demonstrated that concomitant administration of miricorilant with a strong CYP2C19 inhibitor *in vivo* does not lead to excess plasma concentrations of miricorilant, and that no such dose adjustments are needed for the safe administration of miricorilant with other drugs which may inhibit CYP2C19.

EXAMPLE 3 Pharmacokinetics (PK) and metabolism of miricorilant

[0086] 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. 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.

[0087] **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). 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.

[0088] Study 851 (NCT03878264) evaluated the absorption, distribution, metabolism, and excretion (ADME) and mass balance of a single oral dose of [¹⁴C]-miricorilant 150 mg (administered fed) in healthy male volunteers (30–65 years; BMI 18–30 kg/m²). PK and safety were assessed.

[0089] 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.

[0090] 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.

[0091] Drug-drug interaction (DDI) studies were performed in a Phase 1, open-label study evaluating the potential effect of miricorilant (400 mg QD orally on Days 4–12) on the PK of different probes (administered fed) in healthy volunteers (18–60 years; BMI 19–32 kg/m²) (ISRCTN10379288). The following probes were given orally as single doses on Days 1 and 10: repaglinide (0.5 mg), substrate of CYP2C8; rosuvastatin (10 mg), substrate of BCRP; tolbutamide (500 mg), substrate of CYP2C9; midazolam (2.5 mg), substrate of CYP3A4; and dolutegravir (50 mg), substrate of UGT1A1. PK and safety were assessed.

[0092] 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.

[0093] 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).

[0094] In study 850, systemic concentrations increased with repeated dosing with miricorilant 150 mg daily for 14 days in healthy volunteers ($n = 9$). 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 $\text{AUC}_{(0-\text{tau})}$, 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 $\text{AUC}_{(0-\text{inf})}$ (ratio of 0.577), indicating that parent miricorilant was the main circulating species in plasma following oral administration (see FIG. 3).

[0095] As shown in Fig. 3, systemic miricorilant concentrations increased with repeated dosing of miricorilant 150 mg daily for 14 days in healthy volunteers ($n=8$). 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 $\text{AUC}_{(0-24)}$. Accumulation ratios for Days 1 to 14 were 1.68 for C_{max} and 2.17 for $\text{AUC}_{(0-24)}$, with an elimination half-life of 21.6 hours. Following miricorilant dosing at 100 mg, 300 mg, and 900 mg, exposure increased in a close to dose-proportional manner based on C_{max} , $\text{AUC}_{(0-\text{last})}$, and $\text{AUC}_{(0-\text{inf})}$. Miricorilant plasma exposures were approximately 3-fold higher following administration of miricorilant 900 mg under fed versus fasted conditions ($\text{AUC}_{(0-\text{last})}$: 25,200 ng·h/mL vs 7,640 ng·h/mL).

TABLE 5 Time to Steady State Following Miricorilant 150 mg

	Miricorilant 150 mg		
Geometric Mean (Geometric CV%)	Day 1 n=8	Day 7 n=8	Day 14 n=8
C_{max} (ng/mL)	100 (38.2)	142 (63.5)	169 (30.1)
$\text{AUC}_{(0-24)}$ (ng·h/mL)	896 (38.3)	1730 (44.7)	1940 (39.2)

EXAMPLE 4**Effect of Hepatic Impairment on the Pharmacokinetics of Miricorilant: Results from a Phase 1, Open-Label, Adaptive-Design Study**

[0096] 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 (Alkhouiri 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.

[0097] 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) and adult patients with severe hepatic impairment (Child-Pugh Class C) were matched with healthy volunteers based on gender, age (± 10 years), and weight ($\pm 20\%$). Ten healthy volunteers and 9-10 patients each with moderate or severe hepatic impairment (including 4 patients with moderate hepatic impairment 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.

[0098] Pharmacokinetic (PK) results for each cohort are shown in Table 6. The observed effect of moderate or severe hepatic impairment (HI) on miricorilant PK was small. Following a single dose of 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 moderate hepatic impairment compared to healthy matched volunteers. Following a single dose of miricorilant, the geometric mean ratios (90% CI) of miricorilant $AUC_{0-\infty}$ 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. 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 or severe hepatic impairment (n = 9-10) compared to healthy volunteers (n = 10) with normal hepatic function.

TABLE 6

Summary of Statistical Comparisons of Plasma Pharmacokinetic Parameters in patients with hepatic impairment and healthy matched volunteers (600 mg miricorilant)

Analyte	Population	Parameter (units)	n	Impaired ¹ (test)		Control ¹ (reference)		Ratio of Geo. LS Means (%)	90% CI (%)	Inter-Subject CV%
				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.

[0099] Conclusions of Study 854: Miricorilant 600 mg was generally well tolerated in patients with hepatic impairment and in matched healthy volunteers. Moderate or severe hepatic impairment had minimal impact on the PK profile of miricorilant.

[0100] 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 7A 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 7B 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

[0101] These studies characterize the pharmacokinetics and absorption, distribution, metabolism, and excretion (PK/ADME) of miricorilant. Administration of [^{14}C]-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.

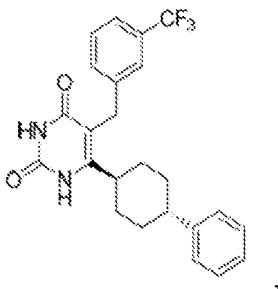
[0102] Conclusions: Miricorilant 600 mg was generally well tolerated in patients with moderate and severe hepatic impairment and in matched healthy volunteers. Hepatic impairment had minimal impact on the systemic plasma exposures (as measured by AUC) of miricorilant. These findings support future inclusion of patients with compensated cirrhotic (stage F4) MASH in the miricorilant clinical development program.

[0103] 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 disorder, said treatment comprising administration of miricorilant, wherein miricorilant is (E)-6-(4-Phenylcyclohexyl)-5-(3-trifluoromethylbenzyl)-1H-pyrimidine-2,4-dione (“miricorilant”), which has the structure:



said miricorilant having a single agent dose that is an amount of miricorilant that is effective to treat said disorder when miricorilant is the only agent administered for said treatment, the method comprising administering to a patient in need of treatment for said disorder:

a) an effective dose of a therapeutic agent, wherein said therapeutic agent is an inhibitor of CYP2C19 enzyme metabolism; and

b) an effective dose of miricorilant, wherein said miricorilant effective dose is substantially the same as said miricorilant single agent dose;

Wherein a) and b) are performed at times effective to provide the patient with an effective level of miricorilant and an effective level of the therapeutic agent at the same time,

Whereby the disorder is treated.

2. The method of claim 1, wherein the amount of miricorilant is between about 10 milligrams ((mg) and about 1000 mg.

3. The method of claim 1, wherein the amount of miricorilant is between about 50 mg and about 1500 mg.

4. The method of claim 1, wherein the CYP2C19 inhibitor is selected from fluvoxamine, N-3-benzyl-nirvanol, loratadine, nootkatone, ticlopidine, armodafinil, chloramphenicol, cimetidine, citalopram, esomeprazole, felbamate, fluconazole, fluoxetine, isoniazid, ketoconazole, luliconazole, modafinil, omeprazole, oritavancin, quercetin, rucaparib, ticlopidine, topiramate, and an oral contraceptive.

5. The method of claim 1, wherein said disorder is a disorder selected from the group of disorders consisting of antipsychotic-induced weight gain and fatty liver disease.
6. The method of claim 1, wherein said disorder is a fatty liver disease selected from non-alcohol related fatty liver disease and an alcohol related liver disease.
7. The method of claim 1, wherein said miricorilant administration is daily administration.
8. The method of claim 1, wherein said miricorilant administration is intermittent administration.
9. The method of claim 1, wherein said miricorilant administration is intermittent administration selected from miricorilant administration every other day, every third day, twice per week, three times per week, and once per week.
10. The method of claim 1, wherein said administration of miricorilant is oral miricorilant administration.
11. The method of claim 1, wherein said miricorilant administration is once daily miricorilant administration.
12. 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.
13. The method of claim 1, wherein miricorilant is administered with food.
14. The method of claim 1, wherein miricorilant is administered to a fasted patient.
15. The concomitant use of miricorilant and a CYP2C19 inhibitor in the treatment of a disorder, wherein said CYP2C19 inhibitor alone has been used in treating said disorder, wherein the amount of miricorilant used in said concomitant treatment with said CYP2C19 inhibitor is substantially the same amount of miricorilant as used alone in treating said disorder.
16. The use of claim 15, wherein the amount of miricorilant is between about 10 milligrams ((mg)) and about 1000 mg.
17. The use of claim 15, wherein the amount of miricorilant is between about 50 mg and about 1500 mg.

18. The use of claim 15, wherein the CYP2C19 inhibitor is selected from fluvoxamine, N-3-benzyl-nirvanol, loratadine, nootkatone, ticlopidine, armodafinil, chloramphenicol, cimetidine, citalopram, esomeprazole, felbamate, fluconazole, fluoxetine, isoniazid, ketoconazole, luliconazole, modafinil, omeprazole, oritavancin, quercetin, rucaparib, ticlopidine, topiramate, and an oral contraceptive.
19. The use of claim 15, wherein said disorder is a disorder selected from the group of disorders consisting of antipsychotic-induced weight gain and fatty liver disease.
20. The use of claim 15, wherein said disorder is a fatty liver disease selected from non-alcohol related fatty liver disease and an alcohol related liver disease.
21. The use of claim 15, wherein said use comprises daily use.
22. The use of claim 15, wherein said use comprises intermittent use.
23. The use of claim 15, wherein said miricorilant use is intermittent use selected from use of miricorilant every other day, every third day, twice per week, three times per week, and once per week.
24. The use of claim 15, wherein said use of miricorilant is oral use.
25. The use of claim 15, wherein said miricorilant use is once daily miricorilant use.
26. The use of claim 15, wherein 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.
27. The use of claim 15, wherein miricorilant is administered with food.
28. The use of claim 15, wherein miricorilant is administered to a fasted patient.