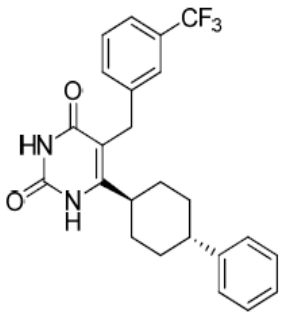
increased levels of the first drug (as compared to the levels obtained by the same dose of the first drug in the absence of the second drug). In this way, the activity of many enzymes may be inhibited by clinically important drugs. Such inhibition may affect the metabolism, and so the blood levels, of 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 named for miricorilant is "CORT118335".

SUMMARY

[0007a] In one aspect, there is provided the use of of (E)-6-(4-Phenylcyclohexyl)-5-(3-trifluoromethylbenzyl)-1H-pyrimidine-2,4-dione ("miricorilant"), which has the structure:



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in the manufacture of a medicament for treating a disorder in a patient, wherein said miricorilant is formulated as a single agent dose containing an amount of miricorilant that is effective to treat said disorder, when miricorilant is the only agent to be administered for said treatment, wherein the patient is to be administered with:

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 the administration of a) and b) are to be 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.

[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.

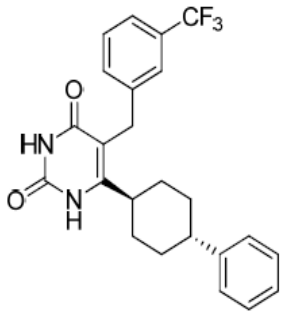
[0009] Surprisingly, Applicant determined that it would be safe to co-administer miricorilant and a strong CYP2C19 inhibitor to human subjects without modifying the miricorilant dose. Applicant discloses herein that miricorilant may be concomitantly administered with a CYP2C19 inhibitor, including with 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 examples, 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

WE CLAIM:

1. Use of (E)-6-(4-Phenylcyclohexyl)-5-(3-trifluoromethylbenzyl)-1H-pyrimidine-2,4-dione ("miricorilant"), which has the structure:



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in the manufacture of a medicament for treating a disorder in a patient, wherein said miricorilant is formulated as a single agent dose containing an amount of miricorilant that is effective to treat said disorder, when miricorilant is the only agent to be administered for said treatment, wherein the patient is to be administered with:

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 the administration of a) and b) are to be 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 use of claim 1, wherein the amount of miricorilant is between about 10 milligrams (mg) and about 1000 mg.

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

4. The use 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 use 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 use 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 use of claim 1, wherein said miricorilant is to be administered daily.

8. The use of claim 1, wherein said miricorilant is to be administered intermittently.

9. The use of claim 8, wherein said intermittent administration is selected from miricorilant administration every other day, every third day, twice per week, three times per week, or once per week.

10. The use of claim 1, wherein said miricorilant is to be administered orally.

11. The use of claim 1, wherein said miricorilant is to be administered once daily.

12. The use 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 use of claim 1, wherein miricorilant is to be administered with food.

14. The use of claim 1, wherein miricorilant is to be administered to a fasted patient.