CONCOMITANT ADMINISTRATION of GLUCOCORTICOID RECEPTOR MODULATOR RELACORILANT and PACLITAXEL, a DUAL SUBSTRATE OF CYP2C8 and CYP3A4

BACKGROUND

[0001] The simultaneous, or nearly simultaneous (e.g., concomitant) presence of two drugs in a subject may alter the effects of one or the other, or both, drugs. Such alterations are termed drug-drug interactions (DDIs). 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 and 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 effective dose of the first drug. Where 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.

[0002] Concomitant administration of different drugs often leads 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 effective concentrations of those drugs as compared to the effective concentrations of those drugs when administered alone. Thus, concomitant administration of drugs may increase the risk of toxic effects of one or both of the co-administered drugs.

[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, designated by a Roman numeral, 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 (Guengerich 208; Zanger and Schwab 2013). These enzymes contribute

to the biotransformation of approximately 70% of clinically used drugs. Generally, these enzymes provide a clearance mechanism for drugs and other xenobiotics and facilitate elimination from the body in urine and/or bile. CYP represents one of nature's most versatile enzymes with respect to its broad substrate profile and types of biotransformation reactions. The individual CYP enzymes exhibit distinct, but sometimes overlapping, substrate and inhibitor selectivities. 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 action on 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).

[0004] Many therapeutically important drugs are metabolized by the CYP enzymes. CYP2C8 substrate drugs include amodiaquine, cerivastatin, dasabuvir, enzalutamide, imatinib, loperamide, montelukast, paclitaxel, pioglitazone, repaglinide, and rosiglitazone (Beckman et al., Pharmacol Rev 68:168-241 (2016)). DDIs between CYP2C8 substrates and other drugs can be significant; Gibbons et al. recommended reducing the dose of enzalutamide to about half the single-agent dose during concomitant use with a potent CYP2C8 inhibitor (Clin Pharmacokinet (2015) 54:1057–1069). Substrates metabolized by CYP3A4 include, for example, midazolam, triazolam, and paclitaxel. Paclitaxel (taxol) is widely used as a chemotherapeutic agent to treat a variety of types of cancer including ovarian, breast, prostate, esophageal, melanoma, and other solid tumor cancers. The primary route of elimination of paclitaxel is through metabolism by both CYP3A4 and CYP2C8. Drug-drug interactions with clopidogrel (a potent CYP2C8 inhibitor) can reduce paclitaxel clearance, leading to increased risk of paclitaxel toxicity, so that "[c]aution should be exercised whenever the simultaneous use of paclitaxel and clopidogrel cannot be avoided" (Bergman et al., Br J Clin Pharmacol (2015) 81(2):313-315). The label for paclitaxel includes a warning that caution should be exercised when paclitaxel is co-administered with a CYP2C8 and/or CYP3A4 inhibitor. Nab-paclitaxel is an albumin bound form of paclitaxel that is associated with fewer side-effects than paclitaxel.

[0005] Relacorilant (see Fig. 1; see also Hunt et al., J. Med. Chem. 60:3405-3421 (2017)) is a selective, non-steroidal modulator of the glucocorticoid receptor that is being investigated in

clinical trials in patients with Cushing's syndrome and in patients with various types of cancer including ovarian cancer and pancreatic cancer.

SUMMARY

[0006] Many therapeutic drugs are substrates of CYP2C8 enzymes, CYP3A4 enzymes, or both; an otherwise safe dose of a first drug metabolized by these CYP enzymes may be a toxic dose when concomitantly administered with a second drug that is an inhibitor of the CYP enzyme. Where a therapeutic drug's primary route of elimination is through metabolism by both CYP2C8 and CYP3A4 enzymes, administration of a concomitant drug that inhibits of both CYP2C8 and CYP3A4 would be expected to cause a substantial increase in the plasma levels of the therapeutic drug by blocking its only elimination pathways. Co-administration with a dual inhibitor of CYP2C8 and CYP3A4 would lead to a greater magnitude of drug-drug interactions (DDIs) versus co-administration with an inhibitor of only one of the enzymes. *In vitro* studies are used to indicate drug combinations expected to suffer from such negative DDIs.

[0007] Relacorilant is believed to be useful in treating many disorders, including cancer and hypercortisolism. Relacorilant is further believed to be useful in combination treatments for cancer and in treating hypercortisolism. *In vitro* tests demonstrated that relacorilant is a potent inhibitor of CYP2C8 (IC_{50} of 0.21 μM) and a potent inhibitor of CYP3A4 (IC_{50} of 1.32 μM). Such potent dual inhibition of both CYP2C8 and CYP3A4 would be expected to increase plasma exposure of dual CYP2C8 and CYP3A4 substrates by more than five-fold when co-administered with relacorilant. Thus, it was expected that significant reductions in doses of dual CYP2C8 and CYP3A4 substrates (e.g., paclitaxel) would be required when administered in combination with relacorilant.

[0008] Upon co-administration with relacorilant such potent inhibition of both CYP2C8 and CYP3A4 by relacorilant would be expected to increase plasma exposure of paclitaxel by blocking its primary pathway of elimination through CYP2C8- and CYP3A4-mediated metabolism. Thus, it was expected that significant reductions in paclitaxel dose would be required when administered in combination with relacorilant. On the basis of relacorilant's expected effect on paclitaxel metabolism, co-administration of paclitaxel and relacorilant would have been expected to require potential reductions in paclitaxel dose by 5-fold or more when paclitaxel is administered with relacorilant.

[0009] Surprisingly, Applicant has discovered that co-administration of paclitaxel and relacorilant does not require such significant reductions in paclitaxel dose. Applicant has discovered that the plasma levels of paclitaxel are not increased by 5-fold or more, but are surprisingly only increased by about 80% (compared to the plasma levels when the same dose of paclitaxel is administered alone) when co-administered with relacorilant.

[0010] Thus, based on *in vitro* potent, dual inhibition of both CYP2C8 and CYP3A4, a significant increase of 5-fold or more in paclitaxel exposure is expected when paclitaxel is administered concomitantly with relacorilant. Surprisingly, Applicant discloses herein that relacorilant and paclitaxel may be concomitantly administered with only a small reduction in the dose of paclitaxel. Accordingly, in contrast to the expected requirement of reductions in paclitaxel dose by 5-fold or more, Applicant discloses herein that relacorilant may be safely administered along with paclitaxel, where the dose of paclitaxel is reduced by about 20% to about 35% (e.g., by about 20%, or by about 25%, or by about 30%, or by about 35%) as compared to the paclitaxel dose that is administered in the absence of relacorilant (typically about 100-125 mg/m^2). Applicant discloses herein that relacorilant may be safely administered along with paclitaxel, where the dose of paclitaxel is reduced to about 80 mg/m^2 (e.g., to about 65 mg mg/m^2, or about 70 mg/m^2, or about 75 mg/m^2, or about 80 mg/m^2, or about 85 mg/m^2, or about 90 mg/m^2, or about 95 mg/m^2) from the paclitaxel dose that is administered in the absence of relacorilant (typically about 100-125 mg/m^2). In embodiments, paclitaxel is administered in the form of nab-paclitaxel. Such concomitant administration of paclitaxel and relacorilant is believed to be safe for the subject and to provide the therapeutic benefits of both drugs to the subject.

[0011] The methods disclosed herein surprisingly provide safe methods for administering drug combinations and dosages that were previously expected to be unsafe, allowing safe and effective concomitant administration of paclitaxel with relacorilant. 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.

BRIEF DESCRIPTION OF THE DRAWING

[0012] Fig. 1 shows the chemical structure of relacorilant ((R)-(1-(4-fluorophenyl)-6-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridine-2-yl)methanone).

DETAILED DESCRIPTION

[0013] Based on the results of standard *in vitro* testing, relacorilant was found to be a potent inhibitor of CYP2C8 and of CYP3A4. These *in vitro* results indicated that co-administration of relacorilant would increase the plasma levels of a CYP2C8 and/or CYP3A4 substrate by greater than 5-fold. Paclitaxel is a substrate for both CYP2C8 and CYP3A4 metabolism. For this reason, co-administration of relacorilant and paclitaxel would thus be expected to greatly increase the concentration of paclitaxel above that concentration obtained when paclitaxel alone was administered. Similar to the *in vitro* results, human clinical studies showed an 8-fold increase in the exposure of midazolam (a standard CYP3A4 substrate) when concomitantly administered with relacorilant. Surprisingly, in human clinical studies conducted in healthy volunteers to evaluate the effect of relacorilant on the concentration of pioglitazone (a standard CYP2C8 substrate), no increase in the concentration of pioglitazone was observed. Also surprisingly, human studies in cancer patients found that co-administration of paclitaxel and relacorilant increased paclitaxel plasma levels only by about 80%, instead of the expected greater increases predicted by the *in vitro* potent, dual inhibition of both CYP2C8 and CYP3A4.

[0014] Applicant discloses herein the surprising discovery that relacorilant may be safely co-administered with paclitaxel with minor dose adjustments. Such small dose adjustments are surprisingly smaller than would be expected based on the greater increases predicted by the *in vitro* potent, dual inhibition of both CYP2C8 and CYP3A4. In embodiments, relacorilant and paclitaxel may be co-administered to a patient in need of treatment, by reducing the paclitaxel dose to about 80 mg/m^2, from a paclitaxel dose of about 100 mg/m^2 to about 125 mg/m^2 that is required for treatment by paclitaxel alone. Relacorilant and paclitaxel may be co-administered to treat cancer, such as ovarian or pancreatic cancer, by reducing the paclitaxel dose to about 80 mg/m^2, from a paclitaxel dose of about 100 mg/m^2 to about 125 mg/m^2 that is required for cancer treatment by paclitaxel alone. Such co-administration of relacorilant and paclitaxel provides therapeutically effective levels of both relacorilant and of paclitaxel at the same time in the patient, while avoiding excessive or toxic doses of either drug.

[0015] In embodiments, Applicant discloses a method of treating cancer, comprising administering to a patient in need of treatment for said cancer:

a) an effective dose of relacorilant; and

b) an effective dose of paclitaxel, wherein said paclitaxel has a single agent dose of about 100 mg/m^2 to about 125 mg/m^2 when administered without other pharmaceutical agents, wherein said effective dose of paclitaxel is reduced by about 20% to about 35% from said single agent dose of paclitaxel when co-administered with relacorilant;

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

Whereby the cancer is treated.

In embodiments, the effective dose of paclitaxel is reduced by about 20%, or by about 25%, or by about 30%, or by about 35%, from said single agent dose of paclitaxel when co-administered with relacorilant. For example, when co-administered with relacorilant, where the effective dose of paclitaxel is a single agent dose of about 100 mg/m^2, the reduced paclitaxel dose may be reduced by about 20% to be about 80 mg/m^2. Where the effective dose of paclitaxel is a single agent dose of about 110 mg/m^2, the reduced paclitaxel dose when co-administered with relacorilant may be reduced by about 20% to be about 88 mg/m^2. Where the effective dose of paclitaxel is a single agent dose of about 120 mg/m^2, the reduced paclitaxel dose when co-administered with relacorilant may be reduced by about 20% to be about 96 mg/m^2. Where the effective dose of paclitaxel is a single agent dose of about 125 mg/m^2, the reduced paclitaxel dose when co-administered with relacorilant may be reduced by about 20% to be about 100 mg/m^2. For further example, where the reduced paclitaxel dose may be reduced by about 25% when co-administered with relacorilant, a single agent dose of paclitaxel of about 100 mg/m^2 would be reduced to be about 75 mg/m^2; a single agent dose of paclitaxel of about 110 mg/m^2 would be reduced to be about 83 mg/m^2; a single agent dose of paclitaxel of about 120 mg/m^2 would be reduced to be about 90 mg/m^2; and a single agent dose of paclitaxel of about 125 mg/m^2 would be reduced to be about 94 mg/m^2. Where the paclitaxel dose may be reduced by about 30% when co-administered with relacorilant, a single agent dose of paclitaxel of about 100 mg/m^2 would be reduced to be about 70 mg/m^2; a single agent dose of paclitaxel of about 110 mg/m^2 would be reduced to be about 77 mg/m^2; a single agent dose of paclitaxel of about 120 mg/m^2 would be reduced to be about 84 mg/m^2; and a single agent dose of paclitaxel of about 125 mg/m^2 would be reduced to be about 88

mg/m^2. Where the paclitaxel dose may be reduced by about 35% when co-administered with relacorilant, a single agent dose of paclitaxel of about 100 mg/m^2 would be reduced to be about 65 mg/m^2; a single agent dose of paclitaxel of about 110 mg/m^2 would be reduced to be about 72 mg/m^2; a single agent dose of paclitaxel of about 120 mg/m^2 would be reduced to be about 78 mg/m^2; and a single agent dose of paclitaxel of about 125 mg/m^2 would be reduced to be about 81 mg/m^2. In embodiments, paclitaxel is administered in the form of nab-paclitaxel.

[0016] In embodiments, Applicant discloses a method of treating cancer, comprising administering to a patient in need of treatment for said cancer:

a) an effective dose of relacorilant; and

b) an effective dose of paclitaxel, wherein said paclitaxel has a single agent dose of about 100 mg/m^2 to about 125 mg/m^2 when administered without other pharmaceutical agents, wherein said effective dose of paclitaxel is between about 65 mg/m^2 to about 95 mg/m^2 when co-administered with relacorilant;

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

Whereby the cancer is treated.

In embodiments, the effective dose of paclitaxel is about 65 mg/m^2, or about 70 mg/m^2, or about 75 mg/m^2, or about 80 mg/m^2, or about 85 mg/m^2, or about 90 mg/m^2, or about 95 mg/m^2. In embodiments, the effective dose of paclitaxel is 80 mg/m^2. In embodiments, paclitaxel is administered in the form of nab-paclitaxel.

[0017] In embodiments, the cancer is ovarian cancer; or pancreatic cancer; or prostate, esophageal, melanoma, and or other solid tumor cancer.

[0018] Applicant's surprising discovery is believed to apply to patients suffering from a disease or disorder treatable by paclitaxel and by relacorilant, such as cancer. For example, patients receiving paclitaxel for the treatment of ovarian cancer or for pancreatic cancer may benefit from concomitant treatment with paclitaxel and relacorilant, and, while receiving relacorilant, may continue to receive paclitaxel by reducing the paclitaxel dose to about 80 mg/m^2 from a paclitaxel dose of about 100 mg/m^2 to about 125 mg/m^2 (the paclitaxel dose required for treatment by paclitaxel alone).

[0019] In embodiments, relacorilant is administered orally. In embodiments, relacorilant, is administered on a daily basis; for example, in embodiments, relacorilant is administered once per day. In embodiments, relacorilant 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 relacorilant is administered. For example, relacorilant may be administered to a patient with a meal, or soon after (e.g., within half an hour) the patient began eating the meal.

[0020] In alternative embodiments, relacorilant 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 relacorilant administration. For example, relacorilant 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.

[0021] In embodiments, relacorilant is administered daily, at a daily dose of relacorilant of between about 1 and 100 mg/kg/day, preferably a daily dose of relacorilant of between about 1 and 20 mg/kg/day. In embodiments, the daily dose of relacorilant 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 relacorilant. In embodiments, a daily dose of relacorilant may be about 10 mg, or 15 mg, or 20 mg, or 25 mg, or 50 mg, or 100 mg, or 150 mg, or 200 mg, or 250 mg, or 300 mg, or 350 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, of 800 mg, or 850 mg, or 900 mg, or 950 mg of relacorilant. In embodiments, an effective dose of relacorilant is between 75 milligrams per day (mg/day) and 200 mg/day, and may be selected from 75 mg/day, 100 mg/day, 125 mg/day, 150 mg/day, 175 mg/day, and 200 mg per day. In embodiments, the effective dose of relacorilant is 100 mg/day, 125 mg/day, or 150 mg/day. In embodiments, the effective dose of relacorilant is 100 mg/day, 125 mg/day, or 150 mg/day. In embodiments, the relacorilant dose may be adjusted (e.g., increased) from an initial dose during the course of treatment.

[0022] In embodiments, paclitaxel is administered as nab-paclitaxel. In embodiments, the dose of nab-paclitaxel is about 60 to about 95 mg/m^2, e.g., about 70 to 90 mg/m^2, and may be administered by intravenous infusion. For example, nab-paclitaxel may be administered at a dose of 80 mg/m^2 administered by intravenous (iv) infusion. Such infusions may be administered intermittently. For example, such infusions may be administered on days 1, 8 and 15 of each 28-day cycle. In embodiments, the dose of nab-paclitaxel is 60 mg/m^2 administered by iv infusion on days 1, 8 and 15 of each 28-day cycle. In embodiments,

relacorilant is administered every day. In embodiments, relacorilant may be administered at a dose of between about 75 to about 250 mg, e.g., at a dose of 100 mg, or 125 mg, or 150 mg, or 175 mg, or 200 mg. In embodiments, relacorilant is administered every day at a dose of 100 mg. In embodiments, relacorilant is administered every day at a dose of 150 mg. In embodiments, e.g., wherein paclitaxel is nab-paclitaxel, relacorilant is administered daily at a dose of 150 mg. In embodiments, e.g., wherein paclitaxel is nab-paclitaxel, relacorilant is administered daily at a dose of 200 mg. In embodiments, e.g., wherein paclitaxel is nab-paclitaxel, relacorilant is administered intermittently (the day before, the day of and the day after the nab-paclitaxel infusion) at a dose of 150 mg. In embodiments, e.g., wherein paclitaxel is nab-paclitaxel, relacorilant is administered intermittently (the day before, the day of and the day after the nab-paclitaxel infusion) at a dose of 200 mg.

DEFINITIONS

[0023] 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.

[0024] 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).

[0025] 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.

[**0026**] 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.

[0027] 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., relacorilant and another drug, which may be, e.g., a drug useful in treating hypercortisolism, may be a drug useful in treating cancer, or another therapeutic agent. In some cases, one agent is administered following a scheduled regimen while the other agent 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.

[0028] As used herein, the terms "intermittent" and “intermittently” refer to administration of doses of a pharmaceutical agent or compound (“drug”) that is other than daily administration; for example, administration of a dose of a compound on alternate days is intermittent administration of the compound. Any schedule of administration less frequently than daily administration is intermittent administration; further examples of intermittent administration include, but are not limited to, e.g., be administration every two days, or every three, or every four days. Intermittent administration also includes, for further examples, administration of a first drug on the day before, the day of and the day after the administration of a second drug; administration of a first drug on day 1, day 15, and day 28 of a repeated cycle of drug administration, which may include administration of a second drug on a different schedule of administration; and other schedules and sequences of drug administration.

[0029] 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 such as relacorilant, pioglitazone, rosiglitazone,

enzalutamide, and others, are typically 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.

[0030] The term "glucocorticoid receptor modulator" (GRM) refers to any compound which modulates GC binding to GR, or which modulates any biological response associated with the binding of GR to an agonist. For example, a GRM that acts as an agonist, such as dexamethasone, increases the activity of tyrosine aminotransferase (TAT) in HepG2 cells (a human liver hepatocellular carcinoma cell line; ECACC, UK). A GRM that acts as an antagonist, such as mifepristone, decreases the activity of tyrosine aminotransferase (TAT) in HepG2 cells. TAT activity can be measured as outlined in the literature by A. Ali *et al.*, J. Med. Chem., 2004, 47, 2441-2452.

[0031] Relacorilant (((R)-(1-(4-fluorophenyl)-6-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridine-2-yl)methanone)) is a GRM. Relacorilant is described in Example 18 of U.S. 8,859,774 (hereby incorporated by reference).

[0032] As used herein, the term "CYP2C8" refers to the cytochrome P450 enzyme subtype 2C8. In humans, the most common form has 490 amino acids, and has the UniProtKB accession number P10632.2. The gene encoding CYP2C8 has Gene ID 1558.

[0033] CYP2C8 substrate drugs include amodiaquine, cerivastatin, dasabuvir, enzalutamide, imatinib, loperamide, montelukast, paclitaxel, pioglitazone, repaglinide, and rosiglitazone (Beckman et al., Pharmacol Rev 68:168-241 (2016)).

[0034] As used herein, the term "CYP3A4" refers to the cytochrome P450 enzyme subtype 3A4. In humans, common isoforms have 503 amino acids (isoform 1) or 502 amino acids (isoform 2), and the protein has the UniProtKB accession number P10632.2. The gene encoding CYP3A4 has Gene ID 1576.

[0035] CYP3A4 substrate drugs include paclitaxel, midazolam and triazolam.

Example 1. In vitro CYP inhibition assay

[0036] Cytochrome P450 (CYP) isoforms CYP2B6, CYP2C8 and CYP3A5, heterologously expressed in *E.coli*, were obtained from Cypex and mixed to produce a 3-CYP mix. In a separate assay, isoforms for CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 heterologously expressed in *E. coli* and obtained from Cypex as a custom made mixture of 5 isoforms. A selective and FDA accepted substrate for each isoform was present in the reaction at a concentration around its K_m.

[0037] Relacorilant (final concentration range 0.032 – 10 µM, 1 % DMSO) or a cocktail of control CYP inhibitors was added to reaction tubes in a 96 well plate format. The CYP mix and a CYP substrate cocktail were added and the tubes warmed for 3 minutes whilst mixing on a BioShake IQ (37°C, 1500 rpm). NADPH (final concentration 1 mM) was added and the mixture was incubated for 10 minutes. Methanol containing an internal standard (1 µM tolbutamide) was then added to all samples, and these were mixed and placed at -20°C for ≥ 1 hour to quench the reaction and allow protein to precipitate.

[0038] All samples were centrifuged (2500 x g, 20 minutes, 4°C). The supernatants were transferred to a fresh 96 well plate, compatible with an autosampler. The plate was sealed with a pre-slit silicone mat and the metabolites were analyzed by LC-MS/MS.

[0039] Control CYP inhibitors (IC_{50} - appropriate concentration range, final assay concentration 1 % DMSO) were added as a cocktail. In Assay 1, the cocktail consisted of CYP2B6, ticlopidine; CYP2C8, quercetin; CYP3A5, ketoconazole. In Assay 1, the cocktail consisted of CYP1A2, α-naphthoflavone; CYP2C9, sulfaphenazole; CYP2C19, tranylcypromine; CYP2D6, quinidine; CYP3A4, ketoconazole.

[0040] In Assay 1, the final concentration of the 3-CYP mix was 18 pmol/mL for CYP2B6 (where pmol is picomoles), 1 pmol/mL for CYP2C and 5 pmol/mL for CYP3A5. In Assay 2, the final concentration of the 5-CYP mix was 32.5 pmol/ml for each of the enzymes evaluated (i.e., CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4).In Assay 1, the CYP substrate cocktail comprised the following components: CYP2B6, bupropion; CYP2C8, amodiaquine; CYP3A5, midazolam. The solvent was methanol for all stock solutions and the final concentration of methanol in the assay was 0.625 %. The metabolites measured were: CYP2B6, hydroxybupropion; CYP2C8, N-desethyl amodiaquine; CYP3A5, 1'-hydroxymidazolam.

[0041] In Assay 2, the CYP substrate cocktail comprised the following components: CYP1A2, tacrine; CYP2C9, diclofenac; CYP2C19, (S)mephenytoin; CYP2D6, bufuralol; CYP3A4, midazolam. The metabolites measured were: CYP1A2, 1-hydroxytacrine; CYP2C9, 4'-hydroxydiclofenac; CYP2C19, 4'-hydroxymephenytoin; CYP2D6, hydroxybufuralol; CYP3A4, 1'-hydroxymidazolam.

[0042] All reactions were performed in duplicate at 37°C and in 0.1 M phosphate buffer (pH 7.4). In Assay 1, the final protein concentration was 0.06 mg/ml. In Assay 2, the final protein concentration was 0.12 mg/ml.

Data processing

[0043] Data were processed and the results reported as an IC_{50} value (concentration resulting in a 50 % inhibition of response), generated from a pseudo-Hill plot, the slope and y axis intercept being used to calculate the IC_{50} according to the following equation.

$$IC_{50} = 10^{\frac{intercept}{slope}}$$

In Assay 1, relacorilant inhibited CYP2C8 with a mean IC_{50} value of 0.21 μM in this assay. In Assay 2, relacorilant inhibited CYP3A4 with a mean IC_{50} value of 1.32 μM.

[0044] Based on the *in vitro* data showing that relacorilant potently inhibited CYP2C8 with a mean IC_{50} value of 0.21 μM, co-administration of a therapeutic concentration of relacorilant with a CYP28 substrate would be expected to result in a greater than 5-fold increase in the plasma exposure of the CYP2C8 substrate, relative to administration of the CYP2C8 substrate alone. Based on the *in vitro* CYP2C8 results, and based on the *in vitro* data showing that relacorilant potently inhibited CYP3CA4 with a mean IC_{50} value of 1.32 μM, co-administration of a therapeutic concentration of relacorilant would be expected to increase the plasma exposure of dual CYP2C8 and CYP3A4 substrates by more than five-fold, relative to administration of the substrate alone.

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

[0045] An open-label, crossover study was conducted in healthy subjects to determine the effect of relacorilant on the plasma exposure of midazolam, a known substrate of CYP3A4, and pioglitazone, a known substrate of CYP2C8. A single dose of midazolam 2.5 mg was administered alone and intensive pharmacokinetic (PK) samples were collected before dosing

(0 hour) and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, and 24 hours post-dose. On the following day, a single dose of 15 mg of pioglitazone was administered alone and intensive PK samples were collected before dosing (0 hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 36, 48, 60, and 72 hours post-dose. Relacorilant 350 mg was then administered once a day for 9 consecutive days. On the tenth day of once-daily relacorilant dosing, a single dose of midazolam 2.5 mg was administered in combination with relacorilant 350 mg and intensive PK samples were again collected at pre-dose though 24 hours post-dose. On the following day, a single dose of 15 mg of pioglitazone was administered in combination with relacorilant 350 mg and intensive pharmacokinetic (PK) samples were again collected at pre-dose through 72 hours post-dose. The plasma concentrations of midazolam and its metabolite, 1-OH midazolam, and pioglitazone and its metabolite, pioglitazone M4 were evaluated by validated bioanalytical assays on each of dosing occasions of midazolam or pioglitazone.

[0046] The PK results showed that once daily dosing of relacorilant increased the plasma exposures (AUC_{inf}) of midazolam and its metabolite by >8-fold, relative to midazolam alone, confirming potent inhibition of CYP3A4 in vivo (Table 1). However, the PK results also showed that once daily dosing of relacorilant did not increase the plasma exposures of pioglitazone or its metabolite, indicating a lack of an inhibitory effect of relacorilant on CYP2C8 (Table 2). Although CYP2C8 inhibition by relacorilant had been previously observed *in vitro*, the results of the clinical drug interaction study demonstrated that relacorilant does not inhibit CYP2C8 *in vivo*.

Table 1 Statistical Comparisons of Plasma Midazolam and its Metabolite Pharmacokinetic Parameters: Day 14 (Treatment D) vs Day 1 (Treatment A) (PK Population)

Parameter (unit)	Test (Day 14) Treatment D		Reference (Day 1) Treatment A		Ratio of Geometric LSMs (%)	90% Confidence Intervals
	Geometric LSM	n	Geometric LSM	n		
Midazolam						
C_{max} (ng/mL)	36.85	26	11.85	27	310.98	271.96 - 355.61
AUC_{0-tz} (ng·h/mL)	271.5	26	30.91	27	878.43	762.70 - 1011.7
AUC_{inf} (ng·h/mL)	294.7	26	33.01	25	892.81	774.67 - 1029.0
1-OH midazolam						

C_{max} (ng/mL)	6.657	26	4.038	27	164.86	139.84 - 194.35
AUC_{0-tz} (ng·h/mL)	74.56	26	9.360	27	796.64	695.61 - 912.35
AUC_{inf} (ng·h/mL)	83.72	26	10.28	26	814.51	712.14 - 931.60

ANOVA, analysis of variance; AUC_{inf}, AUC from time 0 extrapolated to infinity; AUC_{0-tz}, AUC from time 0 until the time of the last measurable concentration; C_{max}, maximum plasma concentration; CV%, coefficient of variation; LSM, least squares mean.

Treatment A: Single oral dose of 2.5 mg midazolam hydrochloride administered on Day 1 (Reference).

Treatment D: Single oral dose of 2.5 mg midazolam hydrochloride and 350 mg relacorilant administered on Day 14 (Test).

Parameters were ln-transformed prior to analysis.

Geometric LSMs were calculated by exponentiating the LSMs from the ANOVA.

Ratio of Geometric LSMs=100*(Test/Reference); where Test is Treatment d and Reference is Treatment A.

Table 2 Statistical Comparisons of Plasma Pioglitazone and its Metabolite Pharmacokinetic Parameters: Day 15 (Treatment E) vs Day 2 (Treatment B) (PK Population)

Parameter (unit)	**Test (Day 15) Treatment E**		**Reference (Day 2) Treatment B**		**Ratio of Geometric LSMs (%)**	**90% Confidence Intervals**
	Geometric LSM	**n**	**Geometric LSM**	**n**		
Pioglitazone						
C_{max} (ng/mL)	376.5	26	483.8	27	77.82	69.65 - 86.96
AUC_{0-tz} (ng·h/mL)	3953	26	5290	27	74.71	68.06 - 82.02
AUC_{inf} (ng·h/mL)	4047	25	5408	27	74.83	68.11 - 82.21
Pioglitazone M4						
C_{max} (ng/mL)	253.9	26	237.3	27	106.99	99.70 - 114.81
AUC_{0-tz} (ng·h/mL)	10460	26	10460	27	99.97	94.80 - 105.43
AUC_{inf} (ng·h/mL)	12590	25	12890	26	97.68	92.98 - 102.62

ANOVA, analysis of variance; AUC_{inf}, AUC from time 0 extrapolated to infinity; AUC_{0-tz}, AUC from time 0 until the time of the last measurable concentration; C_{max}, maximum plasma concentration; CV%, coefficient of variation; LSM, least squares mean.

Treatment B: Single oral dose of 15 mg of pioglitazone hydrochloride (Reference).

Treatment E: Single oral dose of 15 mg of pioglitazone hydrochloride and 350 mg relacorilant administered on Day 15 followed by oral doses of 350 mg relacorilant administered QD on Days 16 and 17 (Test).

Parameters were ln-transformed prior to analysis.

Geometric LSMs were calculated by exponentiating the LSMs from the ANOVA.

Ratio of Geometric LSMs=100*(Test/Reference); where Test is Treatment E and Reference is Treatment B.

Example 3. Administration of relacorilant and nab-paclitaxel to patients with advanced pancreatic cancer

[0047] The combination of relacorilant and nab-paclitaxel has been evaluated in patients with advanced solid tumors. As the elimination of nab-paclitaxel is primarily mediated by both CYP3A4 and CYP2C8, the study was specifically designed to include a 1-week nab-paclitaxel lead-in (1 dose of nab-paclitaxel on Day 1) and a 1-week relacorilant lead-in (relacorilant daily for 7 days) before the start of Cycle 1) to assess the potential for a drug-drug interaction. An interaction would be expected because relacorilant was shown to be a potent dual inhibitor of CYP3A and CYP2C8 *in vitro*. The PK results from this study lead-in showed an increase in nab-paclitaxel exposures (AUC ~80% higher) when administered in combination with relacorilant relative to nab-paclitaxel alone (Table 3). This small AUC increase is surprisingly low in view of the greater increases predicted by the *in vitro* potent, dual inhibition of both CYP2C8 and CYP3A4.

Table 3 Mean Pharmacokinetic Parameters for Nab-Paclitaxel Alone or in Combination with Relacorilant

PK Parameter	Nab-paclitaxel 80 mg/m^2 Alone Mean (%CV) (Lead-In Day 1) N=14	Nab-paclitaxel 80 mg/m^2 in Combination with Relacorilant 100 mg Mean (%CV) (Cycle, 1 Day 8) N=24
AUC (ng·h/mL)	2530 (28)	4550 (97)
C_{max} (ng/mL)	3250 (45)	3230 (81)

Source: Study CORT125134-550

[0048] 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.