CENICRIVIROC FOR THE TREATMENT OF FIBROSIS

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Application No. 62/1 14,304, filed February 10, 2015 the contents of which is incorporated herein by reference in its entirety.

FIELD

[0002] The present disclosure relates to cenicriviroc a salt or solvate thereof, pharmaceutical compositions containing the same, methods for the preparation thereof, and their use in the treatment of inflammation and connective tissue diseases and disorders, especially fibrosis, peritonitis, and liver injury.

BACKGROUND

[0003] Cenicriviroc (also known as CVC) is the common name of (S,E)-8-(4-(2-Butoxyethoxy)phenyl)- 1 -(2-methylpropyl)-N-(4-(((1 -propyl- 1 H-imidazol-5-yl)methyl)sulfinyl)phenyl)-l ,2,3,4-tetrahydrobenzo[b]azocine-5-carboxamide. The chemical structure of cenicriviroc mesylate appears in Figure 1. Cenicriviroc binds to and inhibits the activity of the C-C chemokine receptor type 2 (CCR2) and C-C chemokine receptor type 5 (CCR5) receptors (24). These receptors not only play a role in entry of viruses such as Human Immunodeficiency Virus (HIV) into the cell, but also are important for the recruitment of immune cells to sites of injury. Inhibition of this receptor's activity may have an anti-inflammatory effect. More recently, the role that inflammation plays in the development of fibrosis has been examined [30]. It has been shown that C-C chemokine receptor type 2 (CCR2) and CCR5 may play a role in promoting hepatic fibrosis [3, 4, 5, 31 32].

SUMMARY OF THE INVENTION

[0003a] Aspects of the invention are defined in the independent claims. Some optional features of the invention are defined in the dependent claims.

[0004] There is disclosed a method of treating fibrosis or a fibrotic disease or condition in a subject in need thereof comprising administering to the subject a therapeutically effective amount of cenicriviroc or a salt or solvate thereof. The fibrosis or fibrotic disease or condition may be liver fibrosis or renal fibrosis. The liver fibrosis may be associated with non-alcoholic steatohepatitis (NASH). The liver fibrosis may be associated with non-alcoholic fatty liver disease (NAFLD). The liver fibrosis may be associated with emerging cirrhosis. The liver

fibrosis may comprise non-cirrhotic hepatic fibrosis. The subject may be infected by human immunodeficiency virus (HIV). The cenicriviroc or a salt or solvate thereof may be formulated as a pharmaceutical composition comprising cenicriviroc or a salt or solvate thereof and fumaric acid. The subject may have a disease or condition selected from the group consisting of alcoholic liver disease, HIV and HCV co-infection, HCV infection, type 2 diabetes mellitus (T2DM), metabolic syndrome (MS), and a combination thereof.

[0005] There is disclosed a method of treating NASH in a subject in need thereof comprising administering to the subject a therapeutically effective amount of cenicriviroc, or a salt or solvate thereof; wherein the NASH or the liver fibrosis associated with NASH is associated with type 2 diabetes mellitus (T2DM).

[0006] There is disclosed a method of treating NASH in a subject in need thereof comprising administering to the subject a therapeutically effective amount of cenicriviroc, or a salt or solvate thereof; wherein the NASH or the liver fibrosis associated with NASH is associated with metabolic syndrome (MS).

[0007] There is disclosed a method of treating NASH in a subject in need thereof comprising administering to the subject a therapeutically effective amount of cenicriviroc, or a salt or solvate thereof; wherein liver fibrosis is associated with HIV and HCV co-infection.

[0008] There is disclosed a method of treating NASH in a subject in need thereof comprising administering to the subject a therapeutically effective amount of cenicriviroc, or a salt or solvate thereof; wherein liver fibrosis is associated with HCV infection

[0009] There is disclosed a method of treatment, wherein the cenicriviroc or a salt or solvate thereof is formulated as an oral composition.

[0010] There is disclosed a method of treatment, wherein the cenicriviroc or a salt or solvate thereof is administered once per day or twice per day.

[0011] There is disclosed a method of treatment, wherein the cenicriviroc or a salt or solvate thereof is co-administered with one or more additional active agents. The one or more additional active agents may be one or more antiretroviral agents selected from the group consisting of entry inhibitors, nucleoside reverse transcriptase inhibitors, nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, integrase strand transfer inhibitors, maturation inhibitors, and combinations thereof. The one or more additional antiretroviral agents may be selected from the group consisting of lamivudine, efavirenz, raltegravir, vivecon, bevirimat, alpha interferon, zidovudine, abacavir, lopinavir, ritonavir, tenofovir, tenofovir disoproxil, tenofovir prodrugs, emtricitabine,

elvitegravir, cobicistat, darunavir, atazanavir, rilpivirine, dolutegravir, and a combination thereof.

[0012] The one or more additional active agents may be one or more immune system suppressing agents. The one or more additional active agents may be selected from the group consisting of cyclosporine, tacrolimus, prednisolone, hydrocortisone, sirolimus, everolimus, azathioprine, mycophenolic acid, methotrexate, basiliximab, daclizumab, rituximab, anti-thymocyte globulin, anti-lymphocyte globulin, and a combination thereof.

[0013] The one or more additional active agents may be one or more anti-fibrotic agents including, but not limited to, agents such as N-acetyl-L-cysteine (NAC) as well as angiotensin-converting enzyme (ACE) inhibitors, AT II antagonists, obeticholic acid (OCA), GFT505, simtuzumab, or a combination thereof.

[0014] There is disclosed a method of treatment, comprising detecting a level of one or more biological molecules in the subject treated for fibrosis or the fibrotic disease or condition, and determining a treatment regimen based on an increase or decrease in the level of one or more biological molecules, wherein the biological molecule is selected from the group consisting of lipopolysacchande (LPS), LPs-binding protein (LBP), 16S rDNA, sCD14, intestinal fatty acid binding protein (I-FABP), zonulin-1 , Collagen lal and 3al , TGF-β, fibronectin- 1 , and a combination thereof.

[0015] There is disclosed a method of treatment, comprising detecting a level of one or biological molecules in the subject treated for fibrosis or the fibrotic disease or condition, wherein an increase or decrease in the level of one or more biological molecules compared to a predetermined standard level is predictive of the treatment efficacy of fibrosis or the fibrotic disease or condition, wherein the biological molecule is selected from the group consisting of lipopolysacchande (LPS), LPs-binding protein (LBP), 16S rDNA, sCD14, intestinal fatty acid binding protein (I-FABP), zonulin- 1 , Collagen lal and 3al , TGF-β, fibronectin- 1 , and a combination thereof.

[0016] The one or more biological molecules may be measured in a biological sample from a subject treated for fibrosis or the fibrotic disease or condition. The biological sample may be selected from blood, skin, hair follicles, saliva, oral mucous, vaginal mucous, sweat, tears, epithelial tissues, urine, semen, seminal fluid, seminal plasma, prostatic fluid, pre-ejaculatory fluid (Cowper's fluid), excreta, biopsy, ascites, cerebrospinal fluid, lymph, brain, and tissue extract sample or biopsy sample.

[0017] There is disclosed a method of treating peritonitis in a subject in need thereof comprising administering to the subject a therapeutically effective amount of cenicriviroc or a

salt or solvate thereof. There is also provided cenicriviroc or a salt or solvate thereof for use in the treatment of peritonitis in a subject in need thereof. There is also provided the use of a therapeutically effective amount of cenicriviroc or a salt or solvate thereof for the manufacture of a medicament for use in the treatment of peritonitis in a subject in need thereof. The peritonitis may be infected or non-infected. The peritonitis may be associated with a perforation of the gastrointestinal tract. The peritonitis may be associated with leakage of fluid into the peritoneum. The peritonitis may be associated with a foreign body.

[0018] There is provided a method of treating infected peritonitis in a subject in need thereof comprising administering to the subject a therapeutically effective amount of cenicriviroc, or a salt or solvate thereof.

[0019] The cenicriviroc, or a salt or solvate thereof, may be administered in conjunction with one or more additional peritonitis treatments and/or agents. The additional active agent may be one or more antibiotics. The one or more additional antibiotics may be selected from the group consisting of penicillins, cephalosporins, macrolides, fluoroquinolones, sulfonamides, tetracyclines, and aminoglycosides or a combination thereof.

[0020] There is provided a method of treating liver damage in a subject in need thereof comprising administering to the subject a therapeutically effective amount of cenicriviroc or a salt or solvate thereof. There is provided cenicriviroc or a salt or solvate thereof for use in the treatment of acute liver injury in a subject in need thereof. There is provided the use of coadministration of a therapeutically effective amount of cenicriviroc or a salt or solvate thereof for the manufacture of a medicament for use in the treatment of acute liver injury in a subject in need thereof. The liver damage may be acetaminophen-induced acute liver injury. The liver damage may be drug-induced liver injury. The liver damage may be alcohol-induced liver injury. The liver damage may be chemical-induced liver injury. The liver damage may be toxin-induced liver injury. The cenicriviroc, or a salt or solvate thereof, may be administered in conjunction with one or more additional treatments and/or agents for liver damage. The one or more additional active agents may be n-acetylcysteine (Acetylcysteine; NAC). The NAC may be administered intravenously. The NAC may be administered orally. The one or more additional agent may be a glucocorticoid. The one or more additional agent may be a phosphodiesterase inhibitor.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] Figure 1 is the chemical formula of cenicriviroc mesylate.

[0022] Figure 2 is a graph comparing the absolute bioavailability, in beagle dogs, of cenicriviroc mesylate compounded as an oral solution with that of cenicriviroc mesylate prepared by wet granulation and mixed with various acid solubilizer excipients.

[0023] Figure 3 is a graph of the total impurity and degradant content of different cenicriviroc formulations subjected to accelerated stability testing at 40° C and 75% relative humidity when packaged with a desiccant.

[0024] Figure 4 is a dynamic vapor sorption isotherm for different cenicriviroc formulations.

[0025] Figure 5 shows the absorption of cenicriviroc from different formulations at three pre-treatment states in beagle dogs.

[0026] Figure 6 shows the beagle dog absolute bioavailability of cenicriviroc and lamivudine in combination tablets.

[0027] Figure 7A-B shows intracellular HIV DNA levels in the PBMCs of participants in Study 202 at 24 weeks. Scatter plot depicting fold change in intracellular HIV DNA levels between baseline and 24 weeks, separated by treatment group. The lines and error bars represent mean and standard error measurements, respectively. Fold change was calculated using ΔΔOT in HIV/GAPDH multiplexed qPCR reactions, with each patient's baseline sample as a calibrator. A)

secrete CCL2 which leads to monocyte and macrophage infiltration into the liver. Additionally, CCL2 promotes monocytic hematopoiesis in the bone marrow increasing the pool of circulating monocytes/macrophages. The macrophages in the liver then secrete pro-inflammatory cytokines such as TNF-α and IFN-γ [1].

Embodiments of Therapeutic Utilities:

[00114] The present disclosure provides methods of treating fibrosis. Anti-fibrotic effects of CVC in animal studies were observed when CVC treatment was initiated at the onset of liver injury (TAA) or soon after (TAA; HFD) but not once cirrhosis was established (TAA). This suggests that anti-fibrotic effects of CVC may be more pronounced in populations with established liver fibrosis and at significant risk of disease progression. These include: Non-alcoholic hepatosteatosis (NASH) associated with type 2 diabetes mellitus (T2DM) and metabolic syndrome (MS); HIV and HCV co-infection, or HCV infection.

NASH

[00115] The compositions of the invention may be used to treat liver fibrosis resulting from Nonalcoholic Steatohepatitis (NASH), a common liver disease that affects 2 to 5 percent of Americans. Although liver damage due to NASH has some of the characteristics of alcoholic liver disease, it occurs in people who drink little or no alcohol. The major feature in NASH is fat in the liver, along with inflammation and hepatocyte damage (ballooning). NASH can be severe and can lead to cirrhosis, in which the liver is permanently damaged and scarred and no longer able to work properly. Nonalcoholic fatty liver disease (NAFLD) is a common, often "silent", liver disease associated with obesity related disorders, such as type-2 diabetes and metabolic syndrome, occurring in people who drink little or no alcohol and is characterized by the accumulation of fat in the liver with no other apparent causes. [32-43] At the beginning of the NAFLD spectrum is simple steatosis, which is characterized by a build-up of fat within the liver. Liver steatosis without inflammation is usually benign and slow or non-progressive. NASH is a more advanced and severe subtype of NAFLD where steatosis is complicated by liver-cell injury and inflammation, with or without fibrosis.

[00116] The rising prevalence of obesity-related disorders has contributed to a rapid increase in the prevalence of NASH. Approximately 10% to 20% of subjects with NAFLD will progress to NASH [44].

[00120] In further embodiments, liver fibrosis is associated with emerging cirrhosis. In some embodiments, the cirrhosis is associated with alcohol damage. In further embodiments, the cirrhosis is associated with a hepatitis infection, including but not limited to hepatitis B and hepatitis C infections, primary biliary cirrhosis (PBC), primary sclerosing cholangitis, or fatty liver disease. In some embodiments, the present invention provides for methods of treating subjects at risk of developing liver fibrosis or cirrhosis.

[00121] In another embodiment, the fibrosis comprises non-cirrhotic hepatic fibrosis. In another further embodiment, the subject is infected by human immunodeficiency virus (HIV). In yet a further embodiment, the subject is infected with a hepatitis virus, including but not limited to HCV (hepatitis C virus). In further embodiment, the subject has diabetes. In a further embodiment, the subject has type 2 diabetes. In a further embodiment, the subject has type 1 diabetes. In a further embodiment, the subject has metabolic syndrome (MS). In further embodiments, the subject has one or more of these diseases or disorders. In a further embodiment, the subject is at risk of developing one or more of these diseases. In a further embodiment, the subject has insulin resistance. In further embodiments, the subject has increased blood glucose concentrations, high blood pressure, elevated cholesterol levels, elevated triglyceride levels, or is obese. In a further embodiment, the subject has Polycystic ovary syndrome.

[00122] In one embodiment, the disclosure provides a method of treatment, wherein the cenicriviroc or a salt or solvate thereof is coadministered with one or more additional active agents. In a further embodiment, the one or more additional active agents are one or more antiretroviral agents selected from entry inhibitors, nucleoside reverse transcriptase inhibitors, nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, integrase strand transfer inhibitors, maturation inhibitors, and combinations thereof. In a further embodiment, the one or more additional antiretroviral agents are selected from the group consisting of lamivudine, efavirenz, raltegravir, vivecon, bevirimat, alpha interferon, zidovudine, abacavir, lopinavir, ritonavir, tenofovir, tenofovir disoproxil, tenofovir prodrugs, emtricitabine, elvitegravir, cobicistat, darunavir, atazanavir, rilpivirine, dolutegravir, and a combination thereof. In a further embodiment, the one or more additional active agents are one or more immune system suppressing agents. In a further embodiment, the one or more additional active agents are selected from the group consisting of cyclosporine, tacrolimus, prednisolone, hydrocortisone, sirolimus,

everolimus, azathioprine, mycophenolic acid, methotrexate, basiliximab, daclizumab, rituximab, anti-thymocyte globulin, anti-lymphocyte globulin, and a combination thereof.

[00123] Certain embodiments include methods for monitoring and/or predicting the treatment efficacy of the present treatment as described herein. Such methods include detecting the level of one or more biological molecules, such as for example, biomarkers, in a subject (or in a biological sample from the subject) treated for fibrosis or a fibrotic disease or condition, wherein an increase or decrease in the level of one or more biological molecules compared to a predetermined standard level indicates or is predictive of the treatment efficacy of the present treatment.

[00124] In one embodiment, the disclosure provides a method of treatment, comprising detecting the level of one or more biological molecules in the subject treated for fibrosis or the fibrotic disease or condition, and determining a treatment regimen based on an increase or decrease in the level of one or more biological molecules, wherein the biological molecule is selected from the group consisting of lipopolysaccharide (LPS), LPS-binding protein (LBP), 16S rDNA, sCD14, intestinal fatty acid binding protein (I-FABP), zonulin-1 , Collagen lal and 3al , TGF-β, fibronectin-1 , hs-CRP, IL- I β, IL-6, IL-33, fibrinogen, MCP-1 , MIP- Iα and -1 β, RANTES, sCD163, TGF-β, TNF-a, a biomarker of hepatocyte apoptosis such as CK- 18 (caspase-cleaved and total), or biomarkers of bacterial translocation such as LPS, LBP, sCD14, and I-FABP, or a combination thereof.

[00125] In one embodiment, the disclosure provides a method of treatment, comprising detecting the level of one or biological molecules in the subject treated for fibrosis or the fibrotic disease or condition, wherein an increase or decrease in the level of one or more biological molecules compared to a predetermined standard level is predictive of the treatment efficacy of fibrosis or the fibrotic disease or condition.

[00126] In a further embodiment, the one or more biological molecules are measured in a biological sample from a subject treated for fibrosis or the fibrotic disease or condition. In yet a further embodiment, the biological sample is selected from blood, skin, hair follicles, saliva, oral mucous, vaginal mucous, sweat, tears, epithelial tissues, urine, semen, seminal fluid, seminal plasma, prostatic fluid, pre-ejaculatory fluid (Cowper's fluid), excreta, biopsy, ascites, cerebrospinal fluid, lymph, brain, and tissue extract sample or biopsy sample.

Dosages and Administration:

[00129] A dosage of a particular subject can be determined according to the subject's age, weight, general health conditions, sex, meal, administration time, administration route, excretion rate and the degree of particular disease conditions to be treated by taking into consideration of these and other factors.

[00130] The present disclosure provides a method of treatment, wherein the cenicriviroc or a salt or solvate thereof is formulated as an oral composition.

[00131] The present disclosure provides a method of treatment, wherein the cenicriviroc or a salt or solvate thereof is administered, for example, once per day or twice per day. The dosage form can be administered for a duration of time sufficient to treat the fibrotic disease or condition.

[00132] In the case of oral administration, a daily dosage is in a range of about 5 to 1000 mg, preferably about 10 to 600 mg, and more preferably about 10 to 300 mg, most preferably about 15 to 200 mg as the active ingredient (i.e. as the compound of the invention) per an adult of body weight of 50 kg, and the medicine may be administered, for example, once, or in 2 to 3 divided doses a day.

[00133] The cenicriviroc or a salt or solvate thereof may be formulated into any dosage form suitable for oral or injectable administration. When the compound is administered orally, it can be formulated into solid dosage forms for oral administration, for example, tablets, capsules, pills, granules, and so on. It also can be formulated into liquid dosage forms for oral administration, such as oral solutions, oral suspensions, syrups and the like. The term "tablets" as used herein, refers to those solid preparations which are prepared by homogeneously mixing and pressing the compounds and suitable auxiliary materials into circular or irregular troches, mainly in common tablets for oral administration, including also buccal tablets, sublingual tablets, buccal wafer, chewable tablets, dispersible tablets, soluble tablets, effervescent tablets, sustained-release tablets, controlled-release tablets, enteric-coated tablets and the like. The term "capsules" as used herein, refers to those solid preparations which are prepared by filling the compounds, or the compounds together with suitable auxiliary materials into hollow capsules or sealing into soft capsule materials. According to the solubility and release property, capsules can be divided into hard capsules (regular capsules), soft capsules (soft shell capsules), sustained-release capsules, controlled-release capsules, enteric-coated capsules and the like. The term "pills" as used herein, refers to spherical or near-spherical solid preparations which are prepared by mixing the

added to blood for transfusion or blood derivatives along with one or more agents that purge latent HIV reservoirs, infection and proliferation of the virus can be prevented or controlled. Especially, when blood derivatives are stored, infection and proliferation of the virus is effectively prevented or controlled by addition of the compound of the present invention. In addition, when blood for transfusion or blood derivatives contaminated with HIV virus are administered to a person, infection and proliferation of the virus in the person's body can be prevented by adding the compound of the invention to the blood or blood derivatives in combination with one or more agents that purge latent HIV reservoirs. For example, usually, for preventing HIV infectious disease upon using blood or blood derivatives by oral administration, a dosage is in a range of about 0.02 to 50 mg/kg, preferably about 0.05 to 30 mg/kg, and more preferably about 0.1 to 10 mg/kg as the CCR5/CCR2 antagonist per an adult of body weight of about 60 kg, and the medicine may be administered once or 2 to 3 doses a day. As a matter of course, although the dosage range can be controlled on the basis of unit dosages necessary for dividing the daily dosage, as described above, a dosage of a particular subject can be determined according to the subject's age, weight, general health conditions, sex, meal, administration time, administration route, excretion rate and the degree of particular disease conditions to be treated by taking into consideration of these and other factors. In this case, the administration route is also appropriately selected and, the medicine for preventing HIV infectious disease may be added directly to blood for transfusion or blood derivatives before transfusion or using blood derivatives. In such a case, desirably, the medicine is mixed with blood or blood derivatives immediately to 24 hours before, preferably immediately to 12 hours before, more preferably immediately to 6 hours before transfusion or using blood derivatives.

[00140] Aside from blood for transfusion or blood derivatives, when the compositions of the invention is administered together with the blood for transfusion or blood derivatives and/or other active agents, the medicine is administered preferably at the same time of, to 1 hour before transfusion or using the blood derivatives. More preferably, for example, the medicine is administered once to 3 times per day and the administration is continued 4 weeks.

Combination Therapy:

[00141] The compound of the invention may be used alone or in combination with one or more additional active agents. The one or more additional active agents may be any compound, molecule, or substance which can exert therapeutic effect to a subject in need thereof. The one or

CLAIMS

1. The use of a therapeutically effective amount of cenicriviroc or a salt or solvate thereof in the manufacture of a medicament for treating peritonitis in a subject in need thereof.

2. The use of claim 1, wherein the peritonitis is infected or non-infected.

3. The use of claim 1 or claim 2, wherein the cenicriviroc or a salt or solvate thereof is formulated as a pharmaceutical composition comprising cenicriviroc or a salt or solvate thereof and fumaric acid.

4. The use of claim 1, wherein the peritonitis is associated with a perforation of the gastrointestinal tract.

5. The use of claim 1, wherein the peritonitis is associated with leakage of fluid into the peritoneum.

6. The use of claim 1, wherein the peritonitis is associated with a foreign body.

7. The use of a therapeutically effective amount of a pharmaceutical composition of cenicriviroc or a salt or solvate thereof and fumaric acid in the manufacture of a medicament for treating acute liver injury in a subject in need thereof,

wherein the pharmaceutical composition comprises fumaric acid at a weight ratio of cenicriviroc or a salt or solvate thereof to fumaric acid from about 7:10 to about 10:7.

8. The use of claim 7, wherein the acute liver injury is alcohol-induced, acetaminophen-induced, toxin-induced, and/or chemical-induced liver injury.

9. The use of any of the preceding claims, wherein the cenicriviroc or salt or solvate thereof is formulated as an oral composition.

10. The use of any of the preceding claims, wherein the cenicriviroc or salt or solvate thereof is to be co-administered with one or more additional active agents or treatments.

11. The use of claim 10, wherein the one or more additional active agents or treatments are one or more antibiotic, glucocorticoid, corticosteroid, Pentoxyfylline, phosphodiesterase inhibitor, anti-TNFα agent, and anti-oxidants.

12. The use of claim 11, wherein the one or more antibiotics is selected from the group consisting of penicillins, cephalosporins, macrolides, fluoroquinolones, sulphonamides, tetracyclines, and aminoglysocides or a combination thereof.

13. The use of claim 10, wherein the one or more additional active agents or treatments is n-acetylcysteine (Acetylcysteine; NAC).

14. The use of claim 13, wherein the NAC is to be administered intravenously.

15. The use of claim 13, wherein the NAC is to be administered orally.