Figure 7B is a bar graph showing the pathway enrichment of genes regulated by the combination of OCA + low dose fenofibrate against monotherapy in APOE*3Leiden.CETP mice.

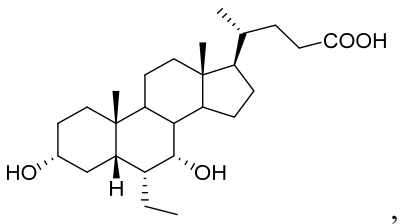
Figure 8 is a graph showing the effect of OCA and a combination of a statin(s) on LDL cholesterol in humans.

SUMMARY

The present application relates to a pharmaceutical composition comprising (i) a first compound, (ii) at least one PPAR-alpha agonist, PPAR-delta agonist, and/or PPAR-alpha and delta dual agonist, and (iii) optionally one or more pharmaceutically acceptable carriers, wherein the first compound is an FXR agonist.

In one aspect of the present disclosure, there is provided a use of a pharmaceutical composition comprising an FXR agonist, at least one fibrate, and optionally one or more pharmaceutically acceptable carriers in the manufacture of a medicament for treating or preventing an FXR mediated disease or condition, wherein:

the FXR agonist is the compound of formula (1):



,

or a pharmaceutically acceptable salt or amino acid conjugate thereof,

wherein the pharmaceutical composition does not comprise any therapeutic agent other than the FXR agonist and

the at least one fibrate; and

wherein the FXR mediated disease or condition is selected from:

(a) primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), portal hypertension, bile acid diarrhea, a chronic liver disease, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), hepatitis C infection, an alcoholic liver disease, liver damage due to progressive fibrosis, liver fibrosis, a cardiovascular disease, and hyperlipidemia; or

(b) a cholestatic liver disease selected from primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), drug-induced cholestasis, hereditary cholestasis, biliary atresia, and intrahepatic cholestasis of pregnancy.

The present disclosure also relates to a pharmaceutical composition comprising (i) a first compound, (ii) at least one fibrate, and optionally (iii) one or more pharmaceutically acceptable carriers, wherein the first compound is an FXR agonist.

The present disclosure also relates to a pharmaceutical composition comprising (i) a first compound, (ii) at least one lipid lowering agent, and optionally (iii) one or more pharmaceutically acceptable carriers, wherein the first compound is an FXR agonist.

The present disclosure also relates to a pharmaceutical composition comprising (i) a first compound, (ii) at least one statin, and optionally (iii) one or more pharmaceutically acceptable carriers, wherein the first compound is an FXR agonist.

The present disclosure also relates to a pharmaceutical composition comprising (i) a first compound, (ii) at least one PPAR-alpha agonist, PPAR-delta agonist, and/or PPAR-alpha and delta dual agonist, (iii) at least one lipid lowering agent, and optionally (iv) one or more pharmaceutically acceptable carriers, wherein the first compound is an FXR agonist.

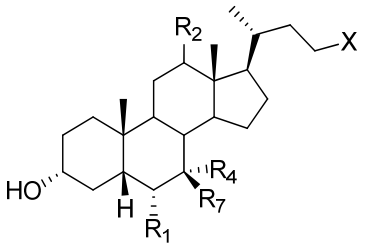
The present disclosure also relates to a pharmaceutical composition comprising (i) a first compound, (ii) at least one fibrate, (iii) at least one lipid lowering agent, and optionally (iv) one or more pharmaceutically acceptable carriers, wherein the first compound is an FXR agonist.

The present disclosure also relates to a pharmaceutical composition comprising (i) a first compound, (ii) at least one PPAR-alpha agonist, PPAR-delta agonist, and/or PPAR-alpha and delta dual agonist, (iii) at least one statin, and optionally (iv) one or more pharmaceutically acceptable carriers, wherein the first compound is an FXR agonist.

The present disclosure also relates to a pharmaceutical composition comprising (i) a first compound, (ii) at least one fibrate, (iii) at least one statin, and optionally (iv) one or more pharmaceutically acceptable carriers, wherein the first compound is an FXR agonist.

The present disclosure also relates to the therapeutic use of the pharmaceutical compositions of the present disclosure.

In one embodiment, the first compound is a compound of formula A:



(A)

or a pharmaceutically acceptable salt or amino acid conjugate thereof, wherein R_1, R_2, R_4, R_7, and X are as defined herein.

The present disclosure also relates to methods for treating or preventing an FXR mediated disease or condition or a disease or condition in which elevated concentrations of circulating lipid compounds in the blood are involved, reducing the level of a liver enzyme, or inhibiting or reversing fibrosis, comprising administering a therapeutically effective amount of a pharmaceutical composition of the present disclosure to a subject in need thereof.

The present disclosure also relates to use of a pharmaceutical composition of the present disclosure for treating or preventing an FXR mediated disease or condition or a disease or condition in which elevated concentrations of circulating lipid compounds in the blood are involved, reducing the level of a liver enzyme, or inhibiting or reversing fibrosis.

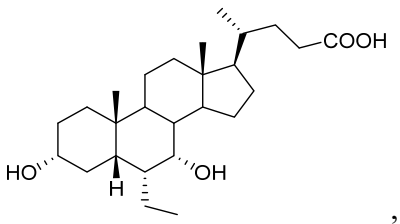
The present disclosure also relates to use of a pharmaceutical composition of the present disclosure in the manufacture of a medicament for treating or preventing an FXR mediated disease or condition or a disease or condition in which elevated concentrations of circulating lipid compounds in the blood are involved, reducing the level of a liver enzyme, or inhibiting or reversing fibrosis.

The compositions and methods of the present disclosure address unmet needs in the treatment or prevention of a disease or disorder in which elevated concentrations of circulating lipid compounds in the blood, such as cholesterol and triglycerides, are involved.

CLAIMS

1. Use of a pharmaceutical composition comprising an FXR agonist, at least one fibrate, and optionally one or more pharmaceutically acceptable carriers in the manufacture of a medicament for treating or preventing an FXR mediated disease or condition, wherein:

the FXR agonist is the compound of formula (1):



,

or a pharmaceutically acceptable salt or amino acid conjugate thereof,

wherein the pharmaceutical composition does not comprise any therapeutic agent other than the FXR agonist and

the at least one fibrate; and

wherein the FXR mediated disease or condition is selected from:

(a) primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), portal hypertension, bile acid diarrhea, a chronic liver disease, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), hepatitis C infection, an alcoholic liver disease, liver damage due to progressive fibrosis, liver fibrosis, a cardiovascular disease, and hyperlipidemia; or

(b) a cholestatic liver disease selected from primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), drug-induced cholestasis, hereditary cholestasis, biliary atresia, and intrahepatic cholestasis of pregnancy.

2. The use of claim 1, wherein the at least one fibrate is selected from bezafibrate, fenofibrate, gemfibrozil, ciprofibrate, clofibrate, and a pharmaceutically acceptable salt or ester thereof.

3. The use of claim 2, wherein the fibrate is bezafibrate.

4. The use of any one of claims 1-3, wherein the FXR agonist is a free acid of the compound of formula (1).

5. The use of any one of claims 1-3, wherein the FXR agonist is a pharmaceutically acceptable salt of the compound of formula (1).

6. The use of any one of claims 1-3, wherein the FXR agonist is a glycine conjugate of the compound of formula (1).

7. The use of any one of claims 1-3, wherein the FXR agonist is a taurine conjugate of the compound of formula (1).

8. The use of any one of claims 1-7, wherein the FXR mediated disease or condition is selected from primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), portal hypertension, bile acid diarrhea, a chronic liver disease, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), hepatitis C infection, an alcoholic liver disease, liver damage due to progressive fibrosis, liver fibrosis, a cardiovascular disease, and hyperlipidemia.

9. The use of any one of claims 1-7, wherein the FXR mediated disease or condition is a cholestatic liver disease selected from primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), drug-induced cholestasis, hereditary cholestasis, biliary atresia, and intrahepatic cholestasis of pregnancy.

10. The use of claim 9, wherein the cholestatic liver disease is PBC.