METHODS OF TREATMENT OF CHOLESTATIC DISEASES

TECHNICAL FIELD

The present invention relates to the field of medicine, in particular the treatment of cholestatic diseases, and more specifically PBC and/or PSC.

BACKGROUND

The present invention is dedicated to cholestasis or cholestatic diseases, also mainly characterized by two distinct pathologies: PBC (Primary Biliary Cholangitis, previously named Primary Biliary Cirrhosis (Beuers et al, 2015)) and/or PSC (Primary Sclerosing Cholangitis).

Cells in the liver produce bile, which passes through ducts within the liver to the gallbladder. Bile is a digestive liquid that is made in the liver. It travels through the bile ducts to the gallbladder and the small intestine, where it helps digest fats and fatty vitamins.

Cholestasis is a condition that results from an impairment of bile formation or bile flow to the gallbladder and duodenum (first section of the small intestine). The effects of cholestasis are profound and widespread, leading to worsening liver disease and systemic illness, liver failure, and the need for liver transplantation.

Cholestasis may be classified as intrahepatic or extrahepatic. Intrahepatic cholestasis primarily involves the bile canaliculi and the intrahepatic bile ducts. Extrahepatic cholestasis involves the extrahepatic ducts, the common hepatic duct or the common bile duct.

Primary Biliary Cholangitis, or PBC, is a chronic inflammatory intrahepatic, or long-term, liver disorder that slowly destroys the small-to-medium-sized bile ducts (tube-like structures that carry bile) within the liver. In patients with PBC, the bile ducts are destroyed by inflammation. This causes bile to remain in the liver, where gradual injury damages liver cells and causes cirrhosis, or scarring of the liver.

PBC is considered as a rare disease, with a prevalence of 40 cases per 100000. The diagnosis of PBC is typically established between the ages of 30 and 60 years. PBC develops in all races, and 90% of cases occur in women. The disease accounts for 2 to 3% of deaths due to cirrhosis (Boonstra et al, 2012; Zetterman, 2015).

Primary Biliary Cholangitis (PBC) was previously named Primary Biliary Cirrhosis, but health officials from around the world have overwhelmingly supported changing the name of Primary Biliary Cirrhosis to Primary Biliary Cholangitis. Since cirrhosis occurs only in the late stage, the name primary biliary cirrhosis is actually a misnomer for patients in the earlier

stages of the illness. Changing the name to primary biliary cholangitis will better serve patients and the medical community worldwide (Beuers et al, 2015).

Although genetic or environmental factors are associated with the risk of PBC, the causes are still unknown, and most experts consider PBC as an autoimmune disease.

PBC advances slowly. Many patients lead active and productive lives for more than 10 to 15 years after diagnosis. Patients who show no symptoms at the time of diagnosis often remain symptom-free for years. Patients who have normal liver tests on treatment may have a normal life expectancy. PBC is a chronic illness and may lead to life-threatening complications, especially after cirrhosis develops.

The first signs being a generalized fatigue (in 70% of cases) and the appearance of pruritus and itching. However, most of the patients are asymptomatic in the early stage of the disease. The diagnosis is established by standard biomedical analyses including the measurement of anti-mitochondrial antibodies (AMAs, which reflect the autoimmune character), and liver enzymes such as alkaline phosphatase.

Ursodeoxycholic acid (UDCA) and Obeticholic acid (OCA) are the only therapies approved by the FDA for the treatment of PBC (Purohit & Cappell, 2015). UDCA is the first line therapy for PBC but is efficient in only 60% of patients. The other 40% respond weakly or not at all to the treatment, and are therefore at high risk of developing cirrhosis, liver insufficiency, and ultimately requiring a liver transplantation.

Primary Sclerosing Cholangitis (PSC) is a chronic, or long-term, disease that slowly damages the extra- and intrahepatic bile ducts. In patients with PBC, the bile ducts are destroyed by inflammation, and in patients with PSC, they become blocked due to inflammation and deteriorating. In both cases, this causes bile to accumulate in the liver, where it gradually damages liver cells and causes cirrhosis, or damage of the liver.

As described for PBC, the cause is still unknown but the immune system is believed to play a major role. About 70 percent of patients are men. It may be related to bacterial or viral infections, as well as problems in the immune system. Genetic factors may also play a role.

PSC is considered an uncommon disease, but recent studies suggest that it may be more common than previously thought. This disease is often associated with inflammatory diseases of the intestine such as hemorrhagic rectocolitis, and accounts for 40% of liver abnormalities related with this disease.

It is a rare disease that affects predominantly men (70% of the patients) with an estimated prevalence of 1 to 5 cases per 10 000 persons.

PSC advances very slowly. Many patients may have the disease for years before symptoms develop. Symptoms may remain at a stable level, they may come and go, or they may

progress gradually. Liver failure may occur 10-15 years after diagnosis, but this may take even longer for some PSC patients. Many people with PSC will ultimately need a liver transplant, typically about 10 years after being diagnosed with the disease. PSC may also lead to bile duct cancer. Endoscopy and MRI tests may be done to monitor the disease.

Many people with PSC do not get symptoms, especially in the early stages of the disease. When symptoms do occur the most common are fatigue, pruritus, or itching of the skin, and jaundice, a yellowing of the skin and eyes. These symptoms may come and go, but they may worsen over time. As the disease continues, the bile ducts may become infected, which can lead to episodes of fever, chills and abdominal pain.

Because many PSC patients have no symptoms, the disease is often discovered through abnormal results on routine liver blood tests. The diagnosis will be completed based on a combination of biochemical, histological and imaging analyses. Formal diagnosis is usually made by cholangiography, an X-ray test involving injection of dye into the bile ducts, or by a MRI.

Although UDCA treatment may be beneficial for some patients, there is currently no therapy that significantly reduces the risk of death or the need for liver transplantation, which still remains the only solution for patient survival.

The need for novel therapeutic options for the management of cholestatic diseases, in particular PSC and/or PBC, is still clear and urgent.

Elafibranor is being developed by Genfit for the treatment of non-alcoholic steatohepatitis. The present inventors herein show that the profile of Elafibranor also makes it a therapeutic asset for the treatment of PBC.

SUMMARY OF INVENTION

A clinical study has surprisingly shown that the treatment of patients with 1-[4-methylthiophenyl]-3-[3,5-dimethyl-4-carboxydimethylmethyloxyphenyl]prop-2-en-1-one (Elafibranor, formely called GFT505) provides a relevant reduction of biochemical markers in the plasma, demonstrating that this compound is advantageous for the treatment of cholestatic diseases.

The present invention relates to elafibranor for use for the treatment of a cholestatic disease.

The present invention also provides the use of elafibranor in the preparation of a pharmaceutical composition for treating a cholestatic disease.

In a further embodiment, the present invention also discloses the use of elafibranor in the manufacture of a medicament for treating a cholestatic disease.

The present invention further relates to a method for treating a cholestatic disease in a subject in need thereof, comprising administering a therapeutic effective amount of elafibranor, in particular thereby inducing a reduction in cholestasis.

In a particular embodiment of the invention, elafibranor is administered at a dose varying between 0.01 mg and 1 g per administration, preferentially from 1 mg to 150 mg per administration, and more preferably from 70 mg to 130 mg. In a particular embodiment, elafibranor is administered once a day. In another particular embodiment, elafibranor is administered once a day at a dose of 80 or 120 mg

The invention also provides a pharmaceutical composition comprising compound elafibranor for use for treating a cholestatic disease.

According to the invention, the pharmaceutical composition may be formulated in the form of injectable suspensions, gels, oils, pills, tablets, suppositories, powders, gel caps, capsules, aerosols or means of galenic forms or devices assuring a prolonged and/or slow release.

In particular, the pharmaceutical composition comprises compound elafibranor and a pharmaceutically acceptable carrier and/or excipient.

In another embodiment of the invention, the invention also discloses a kit for treating a cholestatic disease or for use for treating a cholestatic disease, the kit comprising elafibranor.

According to the present invention, the disclosed method, compound, uses, composition or kit concern the treatment of a cholestatic disease preferably selected in the group consisting in Primary Biliary Cholangitis, Primary Sclerosing Cholangitis, Intrahepatic Cholestasis of Pregnancy, Progressive Familial Intrahepatic Cholestasis, Biliary atresia, Cholelithiasis, Infectious Cholangitis, Cholangitis associated with Langerhans cell histiocytosis, Alagille syndrome, Nonsyndromic ductal paucity, Drug-induced cholestasis, and Total parenteral nutrition – associated cholestasis.

In a preferred embodiment, the cholestatic disease is PBC or PSC.

In another preferred embodiment, the cholestatic disease is PBC.

DESCRIPTION OF THE FIGURES AND TABLES

Abbreviations used in the figures, in the tables, and in the text:

AE	adverse event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AMA	anti-mitochondrial antibody
ASBTi	apical sodium-codependent bile acid transporter inhibitors

AST	Aspartate Aminotransferase
BCL6	B-cell lymphoma 6
C4	serum 7α-hydroxy-4-cholesten-3-one
CDCA	chenodeoxycholic acid
CK-18	cytokeratine-18
CPK	creatine phosphokinase
DCA	deoxycholic acid
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
FGF19	Fibroblast growth factor 19
FXR	Farnesoid X receptor
γGT	gamma-Glutamyl-Transferase
HBV	hepatitis B virus
HCB	hepatitis C virus
HDL-C	High Density Lipoprotein-Cholesterol
HIV	human immunodeficiency virus
IC	informed consent
ICP	Intrahepatic Cholestasis of Pregnancy
IgM	immunoglobulin M
IL-6	interleukin-6
IRB	institutional review board
ITT	Intention To Treat
IVRS	interactive voice response system
IWRS	interactive web response system
LDL-C	Low Density Lipoprotein-Cholesterol
MELD	Model for End Stage Liver Disease
MRI	Magnetic resonance imaging
NASH	nonalcoholic steatohepatitis
NF-κB	nuclear factor kappa B
NOX	NADPH oxidase
OCA	obeticholic acid
PBC	Primary Biliary Chlolangitis
PFIC	Progressive Familial Intrahepatic Cholestasis
PK	pharmacokinetics

PPAR	Peroxisome proliferator-activated receptor
PSC	Primary Sclerosing Cholangitis
QOL	quality of life
TG	TriGlyceride
TGF-β	transforming growth factor beta
TIPS	transjugular intrahepatic portosystemic shunts
TNF-α	tumor necrosis factor alpha
TPN	Total parenteral nutrition
UDCA	ursodeoxycholic acid
ULN	upper limit of normal
VAS	visual analogue score

Figure 1. Dosage of Alkaline Phosphatase

NASH patients treated with both elafibranor doses (80mg and 120mg) improved alkaline phosphatase levels compared to placebo group. Figure 1 shows changes from baseline in liver enzyme in treatment groups of the efficacy evaluable set (n=237). Results are expressed in mean values of changes from baseline during treatment with placebo (n=77), elafibranor 80 mg (n=82) and elafibranor 120 mg (n=78). Error bars represent 95% CIs.

Figure 2 : Dosage of γ-GT

NASH patients treated with both elafibranor doses (80mg and 120mg) improved γ-GT levels compared to placebo group. Figure 2 shows changes from baseline in liver enzyme in treatment groups of the efficacy evaluable set (n=237). Results are expressed in mean values of changes from baseline during treatment with placebo (n=77), elafibranor 80 mg (n=82) and elafibranor 120 mg (n=78). Error bars represent 95% CIs.

Figures 3 : Dosage of C4

Figure 3a: NASH patients treated with both elafibranor doses (80mg and 120mg) improved C4 levels compared to placebo group. Figure 3a shows changes from baseline in treatment groups of the efficacy evaluable set (n=62). Results are expressed in mean values of changes from baseline during treatment with placebo (n=23), elafibranor 80 mg (n=16) and elafibranor 120 mg (n=23).

Figure 3b: Patients treated with both elafibranor doses (80mg and 120mg) improved C4 levels reported to placebo. Figure 3b shows changes from placebo group to treatment groups of the efficacy evaluable set (n=62). Results are expressed in mean values of

changes from baseline during treatment with placebo (n=23), elafibranor 80 mg (n=16) and elafibranor 120 mg (n=23).

DETAILED DESCRIPTION OF THE INVENTION

Cholestasis or cholestatic disease is defined as a decrease in bile flow due to impaired secretion by hepatocytes (hepato-cellular cholestasis) or to obstruction of bile flow through intra- or extrahepatic bile ducts (obstructive cholestasis). In clinical practice, cholestasis is any condition in which the flow of bile from the liver is slowed or blocked.

Examples of cholestatic diseases are Primary Biliary Cholangitis (PBC) (formely named Primary Biliary Cirrhosis), Primary Sclerosing Cholangitis (PSC), Intrahepatic Cholestasis of Pregnancy (ICP), Progressive Familial Intrahepatic Cholestasis (PFIC), Biliary atresia, Cholelithiasis, Infectious Cholangitis, Cholangitis associated with Langerhans cell histiocytosis, Alagille syndrome, Nonsyndromic ductal paucity, Drug-induced cholestasis, Total parenteral nutrition (TPN)–associated cholestasis.

In a particular embodiment, the subject to be treated has PBC. PBC is characterized by changes in many blood biochemical parameters. Patients' sera show the enhanced activity of alkaline phosphatase (ALP), γ-glutamyltransferase (gamma glutamyltranspeptidase, γ-GT), 5'-nucleotidase (5'-NT), and leucineaminopeptidase (LAP), the higher levels of bile acids, cholesterol, phospholipids, copper, γ-globulins, and bilirubin, and the lower level of total protein mainly at the expense of albumin fractions. In PBC, there is a decline in the levels of bile acids, cholesterol, and lecithin in the hepatic bile portion and their simultaneous rises in hepatocytes and blood (Reshetnyak, 2015). Changes in bile acid precursor C4 (7α-hydroxy-4-cholesten-3-one) (C4) can be assessed to characterize PBC.

In a particular embodiment, the patient has PBC and responds at least partly to UDCA. In another embodiment, the patient has PBC and does not respond adequately to UDCA. In a particular embodiment, elafibranor is administered, preferably orally, to a patient with PBC and inadequate response to UDCA, in particular at a dose of 80 or 120 mg.

The term "an effective amount" or "therapeutic effective amount" refers to an amount of the compound sufficient to produce the desired therapeutic result and elafibranor is administered in amounts that are sufficient to display the desired effect. In a particular aspect, the desired effect is an improvement in alkaline phosphatase and/or γ-GT levels signing a reduction in cholestasis. Accordingly, the invention also relates to elafibranor for use in the improvement

of ALP and/or γ-GT levels in a subject in need thereof. In particular, elafibranor is administered for lowering the activity of ALP and/or γ-GT.

In a particular embodiment, elafibranor is administered to a subject with PBC for normalizing ALP, albumin and/or bilirubin level(s).

In a particular embodiment, the subject is with PBC and the treatment results in a level of ALP lower than 1.67 x ULN (upper limit of normal) and total bilirubin within normal limit. The reference range of total bilirubin is 0.2-1.2 mg/dL. The reference range of direct bilirubin is 0.1-0.4 mg/dL. In a particular variant of this embodiment, elafibranor is administered for decreasing ALP level by at least 15%.

In another embodiment, the subject is with PBC and the treatment results in a level of ALP lower than 2 x ULN (upper limit of normal) and total bilirubin within normal limit. In a particular variant of this embodiment, elafibranor is administered for decreasing ALP level by at least 40%.

In a particular embodiment, elafibranor is administered to a subject with PBC, to improve bile acids level such as CDCA, cholic acid, litocholic acid and DCA levels.

In a further embodiment, elafibranor is administered for improving Paris I, Paris II, Toronto I, Toronto II or UK-PBC risk score.

In another embodiment, elafibranor is administered to a subject with PBC for:
- improving AST, γGT, 5'-nucleotidase, total bilirubin, conjugated bilirubin, ALT and albumin levels;
- improving lipid parameters
- improving C4 and/or FGF19 levels
- improving IgM levels; and
- improving 5D-itch scale, PBC 40 QOL, VAS.

The term "treatment" or "treating" refers to therapy, prevention, or prophylaxis of a cholestatic disease in a subject in need thereof. The treatment involves the administration of elafibranor (such as via the administration of a pharmaceutical composition comprising elafibranor) to a subject (e.g. a patient) having a declared disease to prevent, cure, delay, reverse, or slow

down the progression of the disease, improving thereby the condition of patients. A treatment may be also administered to subjects that are either healthy or at risk of developing a cholestatic disease.

The term “subject” refers to a mammal and more particularly a human. The subjects to be treated according to the invention can be appropriately selected on the basis of several criteria associated with cholestatic pathological processes such as previous and/or present drug treatments, associated pathologies, genotype, exposure to risk factors, as well as any other relevant biomarker that can be evaluated by means of any suitable immunological, biochemical, or enzymatic method. The subject to be treated is with PBC, as characterized as follows:

- the presence of at least 2 of the following 3 diagnostic factors:

(i) history of elevated ALP levels for at least 6 months prior to Day 0 (randomization visit)

(ii) positive Anti-Mitochondrial Antibodies (AMA) titers (> 1/40 on immunofluorescence or M2 positive by enzyme-linked immunosorbent assay (ELISA) or positive PBC-specific antinuclear antibodies

(iii) liver biopsy consistent with PBC

- ALP ≥ 1.67x upper limit of normal (ULN)

- optionally, taking UDCA for at least 12 months (stable dose for ≥ 6 months) prior to screening visit.

Elafibranor can have different stable isomeric forms.

Synthesis of elafibranor can for example be carried out as described for compound 29 in WO2004/005233.

Elafibranor can be formulated as pharmaceutically acceptable salts, being slightly- or non-toxic salts obtained from organic or inorganic bases or acids of elafibranor. These salts can be obtained during the final purification step of the compound or by incorporating the salt into the previously purified compound.

The pharmaceutical compositions comprising elafibranor for the treatment of cholestatic diseases can comprise one or several excipients or vehicles, acceptable within a pharmaceutical context (e.g. saline solutions, physiological solutions, isotonic solutions, etc., compatible with pharmaceutical usage and well-known by one of ordinary skill in the art). These compositions can comprise one or several agents or vehicles chosen among dispersants, solubilisers, stabilisers, preservatives, etc. Agents or vehicles useful for these

formulations (liquid and/or injectable and/or solid) are particularly methylcellulose, hydroxymethylcellulose, carboxymethylcellulose, polysorbate 80, mannitol, gelatin, lactose, vegetable oils, acacia, liposomes, etc. These compositions can be formulated in the form of injectable suspensions, gels, oils, pills, suppositories, powders, gel caps, capsules, aerosols, etc., eventually by means of galenic forms or devices assuring a prolonged and/or slow release. For this kind of formulation, agents such as cellulose, carbonates or starches can advantageously be used.

Elafibranor may be administered in an efficient amount by using a pharmaceutical composition as above-defined.

Elafibranor can be administered in different ways and in different forms that allow administering said compounds in a therapeutically effective amount. Thus, for example, it can be administered in a systematic way, per os, by parenteral route, by inhalation, or by injection, such as for example intravenously, by intra-muscular route, by subcutaneous route, by transdermal route, by intra-arterial route, etc. Oral administration is the preferential route of administration for pharmaceutical compositions comprising elafibranor for the treatment of a cholestatic disease.

The frequency and/or dose relative to the administration can be adapted by one of ordinary skill in the art, in function of the patient, the pathology, the form of administration, etc. Typically, elafibranor can be administered for the treatment of a cholestatic disease at doses varying between 0.01 mg and 1 g per administration, preferentially from 1 mg to 150 mg per administration, and more preferably from 70 mg to 130 mg. Administration can be performed daily or even several times per day, if necessary. In a particular embodiment, elafibranor is administered once a day. In another particular embodiment, elafibranor is administered once a day at a dose of 80 or 120 mg.

In a particular embodiment, the invention relates to the use of elafibranor for the treatment of a cholestatic disease, in combination with at least one other therapeutically active agent. The other active agent may in particular be selected from other anti-cholestatic agents such as UDCA or OCA. The invention thus also relates to the combination of elafibranor with UDCA or OCA. The invention also relates to the combination of elafibranor with an anti-cholestatic agent. Other anti-cholestatic agents include, without limitation:

- apical sodium-codependent bile acid transporter inhibitors (ASBTi);
- bile acids;
- cathepsin inhibitors;
- CCR antagonists;
- CD40 inhibitors;

- CD80 inhibitors;
- Dual NOX (NADPH oxidase) 1&4 inhibitors;
- Farnesoid X receptor (FXR) agonists;
- Fibroblast Growth Factor (FGF) 19 recombinant;
- Fractalkine ligand inhibitors;
- ileal sodium bile acid cotransporter inhibitors;
- Monoclonal antibodies;
- PPAR alpha agonists;
- PPAR gamma agonists;
- PPAR delta agonists;
- PPARalpha/gamma agonists;
- PPARalpha/delta agonists;
- PPAR gamma/delta agonists; and
- PPAR alpha/gamma/delta agonists or PPARpan agonists.

Illustrative apical sodium-codependent bile acid transporter inhibitors include, without limitation, A-4250 ; volixibat ; maralixibat formely SHP-625 ; GSK-2330672 ; elobixibat and CJ-14199.

Illustrative bile acids include, without limitation, obeticholic acid and ursodiol (UDCA).

Illlustrative cathepsin inhibitors include, without limitation, VBY-376 ; VBY-825 ; VBY-036 ; VBY-129 ; VBY-285 ; Org-219517 ; LY3000328 ; RG-7236 and BF/PC-18.

Illustrative CCR antagonists include, without limitation, cenicriviroc (CCR2/5 antagonist); PG-092 ; RAP-310 ; INCB-10820 ; RAP-103 ; PF-04634817 and CCX-872.

Illustrative CD40 inhibitors include, without limitation, FFp-104 ; xl-050 ; DOM-0800 ; XmAb-5485 ; KGYY-15 ; FFP-106 ; TDI-0028 and ABI-793.

Illustrative CD80 inhibitors include, without limitation, RhuDex ; FPT-155 ; ToleriMab ; galiximab ; SCH-212394 ; IGM-001 ; ASP-2408 and SCH-204698.

Illustrative dual NOX (NADPH oxidase) 1&4 inhibitors include, without limitation, GKT-831 (formerly GKT137831) and GKT-901.

Illustrative Farnesoid X receptor (FXR) agonists include, without limitation, obeticholic acid ; GS-9674 ; LJN-452 ; EDP-305 ; AKN-083 ; INT-767 ; GNF-5120 ; LY2562175 ; INV-33 ; NTX-023-1 ; EP-024297 ; Px-103 and SR-45023.

Illustrative Fibroblast Growth Factor 19 (FGF-19) recombinants include, without limitation, NGM-282.

Illustrative Fractalkine ligand inhibitors include, without limitation, E-6011 and KAN-0440567.

Illustrative ileal sodium bile acid cotransporter inhibitors include, without limitation, A-4250 ; GSK-2330672 ; volixibat ; CJ-14199 and elobixibat.

Illustrative monoclonal antibodies include, without limitation, bertilimumab ; NGM-313 ; IL-20 targeting mAbs ; fresolimumab (antiTGFβ) formely GC1008 ; timolumab formely BTT-1023 ; namacizumab ; omalizumab ; ranibizumab ; bevacizumab ; lebrikizumab ; epratuzumab ; felvizumab ; matuzumab ; monalizumab ; reslizumab and inebilizumab.

Illustrative PPAR alpha agonists include, without limitation, fenofibrate, ciprofibrate, pemafibrate, gemfibrozil, clofibrate, binifibrate, clinofibrate, clofibric acid, nicofibrate, pirifibrate, plafibride, ronifibrate, theofibrate, tocofibrate and SR10171;

Illustrative PPAR gamma agonists include, without limitation, Pioglitazone, deuterated pioglitazone, Rosiglitazone, efatutazone, ATx08-001, OMS-405 , CHS-131, THR-0921, SER-150-DN, KDT-501, GED-0507-34-Levo, CLC-3001 and ALL-4.

Illustrative PPAR delta agonists include, without limitation, GW501516 (Endurabol or ({4-[({4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazol-5-yl}methyl)sulfanyl]-2-methylphenoxy}acetic acid)) or MBX8025 (Seladelpar or {2-methyl-4-[5-methyl-2-(4-trifluoromethyl- phenyl)-2H-[l,2,3]triazol-4-ylmethylsylfanyl]-phenoxy}-acetic acid) or GW0742 ([4-[[[2-[3-fluoro-4-(trifluoromethyl)phenyl]-4-methyl-5-thiazolyl]methyl]thio]-2-methyl phenoxy]acetic acid) or L165041 or HPP-593 or NCP-1046.

Illustrative PPAR alpha/gamma agonists (also named glitazars) include, without limitation, Saroglitazar, Aleglitazar, Muraglitazar, Tesaglitazar and DSP-8658.

In addition to elafibranor, illustrative PPAR alpha/delta agonists include, without limitation, T913659.

Illustrative PPAR gamma/delta agonists include, without limitation, linoleic acid (CLA) and T3D-959.

Illustrative PPAR alpha/gamma/delta agonists (or “PPARpan agonists”) include, without limitation, IVA337, TTA (tetradecylthioacetic acid), Bavachinin, GW4148, GW9135, Bezafibrat, Lobeglitazone, and CS038.

In a further embodiment, the present invention provides methods of treating a cholestatic disease comprising the administration of elafibranor or the combination of the invention, in particular in the form of a pharmaceutical composition containing this compound.

In another embodiment, the present invention also provides a kit for treating a cholestatic disease comprising elafibranor, optionally in combination to another anti-cholestatic agent as described above.

The invention is further described with reference to the following, non-limiting, examples.

EXAMPLES

Example 1 : ALP and γGT dosages

Adult subjects with non-alcoholic steatohepatitis (age 18-75 years) were treated at the dose of 80mg and 120mg per day of elafibranor over 52 weeks.

A total of 276 NASH patients were randomized: 92 in the placebo group, 93 in the elafibranor 80mg group and 91 in the elafibranor 120mg group. Two patients did not receive the study medication and the remaining 274 patients constitute the ITT (intention to treat) population. 33 patients (12%) dropped out during the study. Final liver biopsies were available in 237 patients (77, 82, and 78 patients in the placebo, elafibranor 80mg, and elafibranor 120mg groups respectively).

Patients were followed every 2 months with clinical and laboratory evaluations.

Patients treated with both elafibranor doses (80mg and 120mg) improved liver function tests (ALT, γGT and alkaline phosphatase) and lipid parameters (triglycerides, LDLcholesterol, HDL-cholesterol).

Elafibranor lowered alkaline phosphatase (see Figure 1) and γ–glutamyl transpeptidase (see Figure 2) in a dose-dependent manner, showing the interest of elafibranor for the treatment of cholestatic diseases.

Beneficial effects of elafibranor on liver function were consistently observed in all patients treated for 1 to 3 months with 80mg/day elafibranor. Significant reductions in circulating levels of γGT and ALP were observed and reached up to -29% for γGT and -25% for ALP in elafibranor treated groups compared to placebo. In addition, in insulin-resistant patients, elafibranor treatment induced a significant reduction in ALT (-20% compared to placebo), while the level of aspartate aminotransferase (AST) was unchanged.

In the Phase 2a and 2b program, elafibranor has consistently shown a significant decrease in liver enzymes, notably in ALP. A decrease in ALP levels is recognized as a particularly relevant surrogate marker for the treatment of PBC, and was recently used as the basis for FDA approval of OCA in this indication.

The subjects show a dose-related improvement in their disease as shown by a decrease in ALP and γGT.

Example 2 : C4 dosage

The effect of elafibranor was further tested in relation to parameters more directly related to cholestatic diseases than ALP and γGT levels. Thus, it was explored whether treated subjects show a decrease in plasma total bile acids. The measurement of serum 7α-hydroxy-4-cholesten-3-one (7α-HCO, or 7αC4, or C4) is a method for monitoring the enzymatic activity of hepatic cholesterol 7α-hydroxylase, the rate-limiting and major regulatory enzyme in the synthesis of bile acids. Thus a decrease in C4 level reflects a decrease in total bile acids in the patient.

In NASH patients with high ALP level at baseline, elafibranor was orally administered at a dose of either 80mg or 120mg per day over 52 weeks.
A total of 62 NASH patients with high ALP levels were randomized: 23 in the placebo group, 16 in the elafibranor 80mg group and 23 in the elafibranor 120mg group.
Bile acids precursor levels were improved in the patients having received both elafibranor doses, in a dose-dependent manner.

Example 3 : clinical trial for PBC

A multicenter, double-blind, randomized, placebo-controlled, phase 2 study clinical trial is conducted in patients with Primary Biliary Cholangitis and inadequate response to ursodeoxycholic acid to evaluate the efficacy and safety of treatment with elafibranor given orally (80mg daily and 120mg daily) for 12 weeks.

Primary objectives

The primary objective is to compare the effect of daily oral administration of elafibranor 80mg and 120 mg on changes in serum alkaline phosphatase (ALP) to that of placebo in patients with PBC and inadequate response to ursodeoxycholic acid (UDCA).

Secondary objectives

The secondary objectives are:

- to assess the response to treatment based on composite endpoints:
  - ALP < 1.67 × upper limit of normal (ULN) and total bilirubin within normal limit and > 15% decrease in ALP
  - ALP < 2 × ULN and total bilirubin within normal limit and > 40% decrease in ALP
- to assess response according to:
  - Paris I, Paris II, Toronto I, Toronto II, UK-PBC risk score

- to assess response based on the percent of patients who normalized ALP
- to assess response based on the percent of patients who normalized albumin
- to assess response based on the percent of patients who normalized bilirubin
- to assess the change from baseline in AST, γGT, 5'-nucleotidase, total bilirubin, conjugated bilirubin, ALT, albumin
- to assess the change from baseline in lipid parameters
- to assess the change from baseline in bile acids: CDCA, cholic acid, litocholic acid, DCA
- to assess the change from baseline in C4, FGF19
- to assess the change from baseline in IgM
- to assess the change from baseline in:
  - 5D-itch scale
  - PBC 40 QOL
  - VAS
- to assess the tolerability and safety of elafibranor in patients with PBC
- to assess pharmacokinetics (PK) of elafibranor 80mg and 120mg and its main metabolite in PBC patients and to explore an exposure-response relationship.

Inclusion criteria

1. Must have provided written informed consent (IC)
2. Males or females 18 to 75 years of age
3. Definite or probable PBC diagnosis as demonstrated by the presence of at least 2 of the following 3 diagnostic factors:
   - History of elevated ALP levels for at least 6 months prior to Day 0 (randomization visit)
   - Positive Anti-Mitochondrial Antibodies (AMA) titers (> 1/40 on immunofluorescence or M2 positive by enzyme-linked immunosorbent assay (ELISA) or positive PBC-specific antinuclear antibodies
   - Liver biopsy consistent with PBC
4. ALP ≥ 1.67x upper limit of normal (ULN)
5. Taking UDCA for at least 12 months (stable dose for ≥ 6 months) prior to screening visit
6. Contraception: Females participating in this study must be of non-childbearing potential or must be using highly efficient contraception for the full duration of the study and for 1 month after the end of treatment, as described below:

a) Cessation of menses for at least 12 months due to ovarian failure
b) Surgical sterilization such as bilateral oophorectomy, hysterectomy, or medically documented ovarian failure
c) If requested by local IRB regulations and/or National laws, sexual abstinence may be considered adequate (the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject)
d) Using a highly effective non-hormonal method of contraception (bilateral tubal occlusion, vasectomised partner or intra-uterine device)
e) Double contraception with barrier and highly effective hormonal method of contraception (oral, intravaginal or transdermal combined estrogen and progestogen hormonal contraception associated with inhibition of ovulation, oral, injectable or implantable progestogen-only hormonal contraception associated with inhibition of ovulation or intrauterine hormone-releasing system). The hormonal contraception must be started at least one month prior to randomization.

7. Must agree to comply with the trial protocol.

Exclusion criteria:

1. History or presence of other concomitant liver diseases including:
   - Hepatitis B or C virus (HCV, HBV) infection
   - Alcoholic liver disease
   - Definite autoimmune liver disease or overlap hepatitis
   - Gilbert's Syndrome (due to interpretability of bilirubin levels)
   - Known history of alpha-1 antitrypsin deficiency
2. Significant renal disease, including nephritic syndrome, chronic kidney disease (defined as patients with markers of kidney damage or estimated glomerular filtration rate [eGFR] of less than 60 mL/min/1.73 m2).
3. Patients with moderate or severe hepatic impairment (defined as Child-Pugh B/C)
4. Platelet count <150 X 10 3/microliter
5. Albumin <3.5 g/dL
6. Presence of clinical complications of PBC or clinically significant hepatic decompensation, including:
   - History of liver transplantation, current placement on a liver transplant list, or current Model for End Stage Liver Disease (MELD) score ≥ 15

- Patients with cirrhosis/portal hypertension and complications (or signs and symptoms of cirrhosis/portal hypertension), including known esophageal varices, poorly controlled or diuretic resistant ascites, history of variceal bleeds or related interventions (e.g., insertion of variceal bands or transjugular intrahepatic portosystemic shunts [TIPS]), and hepatic encephalopathy, history or presence of spontaneous bacterial peritonitis, hepatocellular carcinoma
- Hepatorenal syndrome (type I or II) or screening serum creatinine > 2 mg/dL (178 µmol/L)

7. Administration of the following medications is prohibited as specified below:
   - 2 months preceding screening and throughout the trial (up to the last study visit): fibrates or obeticholic acid, glitazones
   - 3 months prior to screening and throughout the trial (up to the last study visit)): azathioprine, colchicine, cyclosporine, methotrexate, mycophenolate mofetil, pentoxifylline; budesonide and other systemic corticosteroids; and potentially hepatotoxic drugs (including α-methyl-dopa, sodium valproic acid, isoniazide, or nitrofurantoin)
   - 12 months prior to inclusion visit and throughout the trial (up to the last study visit): antibodies or immunotherapy directed against interleukins or other cytokines or chemokines
8. If female: known pregnancy, or has a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating
9. Known history of human immunodeficiency virus (HIV) infection
10. Known hypersensitivity to the investigational product or any of its formulation excipients

Randomization

Patients who satisfy all eligibility criteria will be randomized in a 1:1:1 ratio to one of the following groups:

- Elafibranor 80mg
- Elafibranor 120mg
- Placebo

A central randomization system will be used (interactive voice/web response system [IVRS/IWRS]).

Primary Endpoint

The primary endpoint is the relative change in serum ALP from baseline to end of treatment in each elafibranor arm, compared to placebo

Secondary Endpoint

- Response rate in elafibranor 80mg and 120mg and placebo groups with response defined as ALP less than 1.67 times ULN and total bilirubin within normal limits and ALP reduction > 15%.
- Response rate in elafibranor 80mg and 120mg and placebo groups with response defined as ALP less than 2 times ULN and total bilirubin within normal limits and ALP reduction > 40%
- Response rate according to Paris I, Paris II, Toronto I, Toronto II, UK PBC risk score
- Alkaline phosphatase response rates of 10%, 20% and 40% decrease
- Response rate in elafibranor 80mg and 120mg and placebo groups with response defined as percent of patients with normalized ALP at the end of treatment
- Response rate in elafibranor 80mg and 120mg and placebo groups with response defined as percent of patients with normalized bilirubin at the end of treatment
- Response rate in elafibranor 80mg and 120mg and placebo groups with response defined as percent of patients with normalized albumin at the end of treatment
- Changes from baseline in:
  - Gamma-glutamyl transferase (γGT)
  - Alanine aminotransferase (ALT)
  - Aspartate aminotransferase (AST)
  - 5'-nucleotidase
  - Bilirubin (total and conjugated)
  - Albumin
  - total cholesterol, LDL-chol, HDL-Chol, Triglycerides
  - Bile acids : CDCA, cholic acid, litocholic acid, DCA
  - C4, FGF19
  - IgM
  - Quality of Life: PBC 40 QOL
  - Pruritus: 5-D Pruritus Questionnaire and Visual Analogue Score (VAS)
  - Biomarkers of inflammation and liver fibrosis: TNF-α, TGF-β, IL-6, CK-18 and lysophosphatidic acid
- Plasma concentrations of elafibranor and its main metabolite and exposure-response relationship

- Adverse Events (AEs)
- Cardiovascular parameters (12-lead ECG, heart rate, blood pressure)
- Hematology and safety parameters

It is expected that elafibranor induces a significant reduction in serum ALP from baseline to end of treatment, compared to placebo. In addition, it is expected that elafibranor induces significant improvement in at least one of the secondary endpoints.

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CLAIMS

1. Use of Elafibranor in the manufacture of a medicament for the treatment of a cholestatic disease, wherein said Elafibranor is to be administered at a dose varying between 0.01 mg and 1 g per administration.

2. The use according to claim 1, wherein said Elafibranor is to be administered at a dose varying from 1 mg to 150 mg per administration, and preferably from 70 mg to 130 mg.

3. The use according to claim 1 or 2, wherein said Elafibranor is in the form of a pharmaceutical composition.

4. The use according to claim 3, wherein said composition is formulated in the form of injectable suspensions, gels, oils, pills, suppositories, powders, gel caps, capsules, aerosols or means of galenic forms or devices assuring a prolonged and/or slow release.

5. The use according to any one of the preceding claims, wherein the cholestatic disease is selected in the group consisting of Primary Biliary Cholangitis (PBC), Primary Sclerosing Cholangitis (PSC), Intrahepatic Cholestasis of Pregnancy, Progressive Familial Intrahepatic Cholestasis, Biliary atresia, Cholelithiasis, Infectious Cholangitis, Cholangitis associated with Langerhans cell histiocytosis, Alagille syndrome, Nonsyndromic ductal paucity, Drug-induced cholestasis, and Total parenteral nutrition – associated cholestasis.

6. The use according to claim 5, wherein the cholestatic disease is PBC or PSC.

7. The use according to claim 6, wherein the cholestatic disease is PBC.

8. The use according to any one of claims 1 to 7, wherein said Elafibranor is to be orally administered once daily at a dose of 80 or 120 mg/day, in particular to a patient with PBC with inadequate response to UDCA.

9. The use according to any one of claims 1 to 8, wherein said Elafibranor is to be administered in combination with another anti-cholestatic agent.