non-invasive methods are not available to correctly diagnose NAFLD or NASH and even the histological features are not always sufficient to distinguish properly NAFLD or NASH from other conditions such as alcoholic liver disease (Yeh M et al., 2007, Vuppalanchi R and Chalasani N, 2009).

Means for an effective treatment for liver fibrotic diseases, and NAFLD and NASH in particular, are still insufficient. No treatment is established for patient with NASH, and several therapeutic options are tested in clinical trial (Vuppalanchi R and Chalasani N, 2009, Dowman J.K et al., 2009). These studies involve the use of many different families of chemical compounds (fibrates, thiazolidinediones, biguanides, statins, cannabinoids) and therapeutic targets (nuclear receptors, angiotensin receptors, cannabinoid receptors, HMG-CoA reductase). Recently, studies involving thiazolidinediones (Rosiglitazone and Pioglitazone) have shown that these drugs may improve liver condition but treatment with these drugs is not without undesired effects such as higher risks of congestive cardiac failure and osteoporosis, as well as weight gain with psychological effects on the patient (Dowman J.K et al., 2009; Shiri-Sverdlov R et al., 2006; Neuschwander-Tetri et al., 2003). Clinical trials involving the administration of cannabinoids have raised the concern of neuropsychiatric disruption (Vuppanchi R and Chalasani N, 2009). Other therapies currently ongoing are seeking to assess in NASH drugs as antioxidants but none of these treatments has yet showed convincing results (Nelson A et al., 2009).

Currently there are no approved treatments of NASH, but two compounds with different mechanisms of action are currently in Phase 3 clinical trials – obeticholic acid (OCA, FXR agonist) and Elafibranor.

1-[4-methylthiophenyl]-3-[3,5-dimethyl-4-carboxydimethylmethyloxyphenyl]prop-2-en-1-one (Elafibranor, or ELA formely named GFT505), a PPAR-alpha/delta dual agonist disclosed in WO2004005233, possesses properties which can be advantageous for the treatment of a number of gastroenterology and liver diseases, in particular cholestatic diseases such as PBC (primary biliary cholangitis) and PSC (primary sclerosing cholangitis), or liver diseases, in particular non-alcoholic fatty liver diseases (NAFLD) such as Non-Alcoholic SteatoHepatitis (NASH).

Elafibranor has been tested for clinical efficacy in NASH in a 1-year liver biopsy-based Phase 2b trial (GFT505-2127), one of the largest interventional studies ever conducted in NASH. Administered to over 800 patients and healthy volunteers to date, elafibranor has demonstrated beneficial properties for NASH, including in particular: improvement of markers of liver dysfunction, including ALAT, ASAT, γGT, ALP; improvement of insulin sensitivity and glucose homeostasis; favorable effects on plasma lipids, including decrease of plasma triglycerides and LDL-C, and increase of HDL-C levels; anti-inflammatory properties; efficacy on histological NASH parameters (steatosis, inflammation, fibrosis)

CLAIMS

1. A combination product comprising:

(i) Elafibranor (ELA) or a pharmaceutically acceptable salt thereof; and

(ii) a FXR agonist.

2. The combination product according to claim 1, wherein the FXR agonist is Obeticholic acid (OCA) or a pharmaceutically acceptable salt thereof.

3. The combination product according to claim 1, wherein the FXR agonist is INT-767 or a pharmaceutically acceptable salt thereof.

4. The combination product according to any one of claims 1 to 3, wherein the combination product is a composition comprising (i) and (ii) and a pharmaceutically acceptable carrier.

5. The combination product according to any one of claims 1 to 3, wherein the combination product is a kit of parts comprising (i) and (ii).

6. The combination product according to any one of claims 1 to 5, for sequential, separate or simultaneous use in the treatment of a disease.

7. Use of:

(i) a Elafibranor (ELA) or a pharmaceutically acceptable salt thereof; and

(ii) a FXR agonist,

in the preparation of a medicament for combination therapy for the treatment of an immune, inflammatory, metabolic, fibrotic or cholestatic disease.

8. The use according to claim 7, wherein the FXR agonist is Obeticholic acid (OCA) or a pharmaceutically acceptable salt thereof, or is INT-767 or a pharmaceutically acceptable salt thereof.

9. The use according to claim 7 or 8, wherein the disease is non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), liver fibrosis, liver cirrhosis, primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC).

10. The combination product according to any one of claims 1 to 6, for use in a method for the treatment of an immune, inflammatory, metabolic, fibrotic or cholestatic disease.

11. The combination product for use according to claim 10, wherein the disease is NAFLD, NASH, liver fibrosis, liver cirrhosis, PBC or PSC.

12. The use according to any one of claims 7 to 9, wherein the FXR agonist is Obeticholic acid (OCA) or a pharmaceutically acceptable salt thereof; and wherein:

- ELA is for administration at a dose comprised between 5 and 80 mg/day and OCA is for administration at a dose comprised between 7 and 17 mg/day;
- ELA is for administration at a dose comprised between 40 and 60 mg/day and OCA is for administration at a dose comprised between 5 and 12.5 mg/day;
- ELA is for administration at a dose comprised between 32 and 48 mg/day and OCA is for administration at a dose comprised between 4 and 10 mg/day;
- ELA is for administration at a dose comprised between 27 and 40 mg/day and OCA is for administration at a dose comprised between 3 and 8 mg/day;
- ELA is for administration at a dose comprised between 16 and 24 mg/day and OCA is for administration at a dose comprised between 2 and 5 mg/day; or
- ELA is for administration at a dose comprised between 8 and 12 mg/day and OCA is for administration at a dose comprised between 1 and 2.5 mg/day.

13. Use according to any one of claims 7 to 9 or 12, wherein (i) and (ii) are for separate, sequential or simultaneous administration.

14. The combination product according to any one of claims 1 to 6 or 10 to 11, wherein the FXR agonist is Obeticholic acid (OCA) or a pharmaceutically acceptable salt thereof; and wherein:

- ELA is for administration at a dose comprised between 5 and 80 mg/day and OCA is for administration at a dose comprised between 7 and 17 mg/day;
- ELA is for administration at a dose comprised between 40 and 60 mg/day and OCA is for administration at a dose comprised between 5 and 12.5 mg/day;
- ELA is for administration at a dose comprised between 32 and 48 mg/day and OCA is for administration at a dose comprised between 4 and 10 mg/day;
- ELA is for administration at a dose comprised between 27 and 40 mg/day and OCA is for administration at a dose comprised between 3 and 8 mg/day;

- ELA is for administration at a dose comprised between 16 and 24 mg/day and OCA is for administration at a dose comprised between 2 and 5 mg/day; or

- ELA is for administration at a dose comprised between 8 and 12 mg/day and OCA is for administration at a dose comprised between 1 and 2.5 mg/day.

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