BRIEF DESCRIPTION OF THE ~~INVENTION~~DISCLOSURE

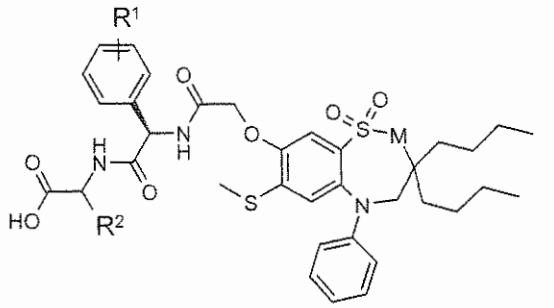
The aim of the present ~~invention~~disclosure is to provide a combination for simultaneous, separate or sequential administration which combination comprises an IBAT inhibitor and a bile acid binder. Such a combination will protect the patient from any possible side effect caused by excess of bile acids in the colon, such as diarrhoea. If the transport of bile acids is blocked by an IBAT inhibitor the bile acids might be deposited in the colon and induce a secretory diarrhoea as an undesired side effect caused by the treatment with an IBAT inhibitor.

In the provided combination therapy the bile acid binder, for instance a resin such as cholestyramine, cholestipol or colesevelam may be administered in a dosage form with colon release of the bile acid binder. A colon release formulation will provide protection of the bile acid binder to the luminal contents in the more proximal parts of the intestine, where the bile acid concentrations are high. Such a formulation will prevent binding of bile acids to the bile acid binder before the formulation reaches the colon. Thereby, maximal bile acid binding capacity will be obtained in the colon and any possible gastro-intestinal side effects, such as diarrhoea, may be avoided. Thus, any additional amount of bile acid presented in the colon due to the treatment with the IBAT inhibitor compound, would be bound to a bile acid binder, which the bile acid binder is preferably delivered in the colon, thereby any possible side effects such as diarrhoea is avoided and maximal excretion of bile acids will be obtained (IBAT blockade of IBAT will let more bile acids pass to colon where they will be bound to bile acid binders resulting in no passive absorption of bile acids from colon). The release of bile acid binders in colon will decrease the needed dose to archive pharmacological effects from the binder.

A further aspect of the ~~invention~~disclosure is that an increased effect can be achieved by binding the unconjugated bile acids in colon and inhibit the uptake in colon. This leads to a further decrease in bile acid levels and an increase in use of cholesterol for bile acid synthesis, resulting in lower levels of cholesterol in plasma.

Further, the colon stimulating effect of bile acids is limited, which leads to decreases the occurrence of diarrhoea. Moreover, bile acid salts are eluated to a greater extent without affecting the absorption of lipid soluble vitamins A, D, E and K in the small bowel. According to one embodiment an increased efficacy is obtained by using an IBAT inhibitor according to formula (I) or formula (II) including compounds of examples 1-14.

In another embodiment, there is provided the use of an IBAT inhibitor of formula II



formula II

wherein

M is $-CH_2$ or NH;

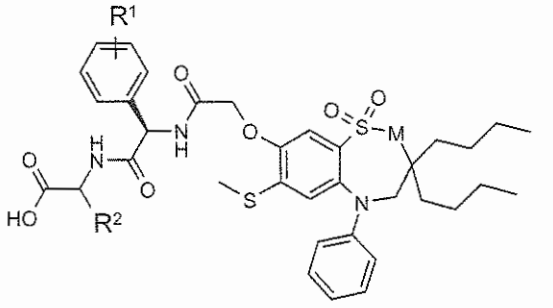
R^1 is H or OH; and

R^2 is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2OH$, CH_2OCH_3, $-CH(OH)CH_3$, $-CH_2SCH_3$, or $-CH_2CH_2$-S-CH_3; or a pharmaceutically acceptable salt thereof,

and a bile acid binder,

wherein the bile acid binder is formulated for colon release, in the manufacture of a medicament for the treatment of a liver disease selected from the group consisting of primary biliary cirrhosis (PBC), progressive familial intrahepatic cholestasis (PFIC), Alagilles syndrome (ALGS), primary sclerosing cholangitis (PSC), non-alcoholic steatohepatitis (NASH) and pruritus of cholestatic liver disease.

In another embodiment, there is provided the use of a pharmaceutical formulation comprising an IBAT inhibitor of formula II



formula II

wherein

M is $-CH_2$ or NH;

R^1 is H or OH; and

R^2 is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH_2OH$, CH_2OCH_3, $-CH(OH)CH_3$, $-CH_2SCH_3$, or $-CH_2CH_2$-S-CH_3; or a pharmaceutically acceptable salt thereof,

and a bile acid binder,

wherein the bile acid binder is in the core and formulated for release in the colon and wherein the IBAT inhibitor is in an outer layer formulated for immediate release or for delayed release in the distal jejunum or the proximal ileum, in the manufacture of a medicament for the treatment of a liver disease selected from the group consisting of primary biliary cirrhosis (PBC), progressive familial intrahepatic cholestasis (PFIC), Alagilles syndrome (ALGS), primary sclerosing cholangitis (PSC), non-alcoholic steatohepatitis (NASH) and pruritus of cholestatic liver disease.