Strong anti-steatotic and anti-fibrotic effects of novel FXR agonists in a murine NASH model that resembles human NASH

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Abstract
Non-Alcoholic Steatohepatitis (NASH) is a liver disease with signs of steatosis, liver inflammation and fibrosis manifested histologically. Metabolic Syndrome, Obesity and hepatic insulin resistance, in particular, are considered as driving factors in the etiology of NASH, therefore any animal model that tries to resemble the human NASH situation has to take these factors into account. Currently, there is no dedicated treatment approved for NASH and due to the growing incidence of this disease in developed countries, there is also an increasing demand for a pharmaceutical that addresses the aforementioned factors. Stetic Institute & Co, has developed a novel murine model for NASH that closely mimics the human NASH situation in the sense that the animals display major hallmarks of human NASH including a moderate increase in transaminases and plasma lipids. The animals develop the entire cascade of metabolically induced liver disease from fatty liver / steatosis over NASH, to fibrosis, cirrhosis and ultimately hepatocellular carcinoma (HCC). Phenex AG has developed novel potent non-steroidal FXR agonists with a good pharmacokinetic profile that were tested in the Stetic mouse NASH model. We used three different administration regimes from five (5) to sixteen (16) weeks of administration to test for preventive as well as for curative effects. As an outcome, our new FXR agonists Px20350 and Px20606 show superior effects at doses of 10 and 30 mpk/d in reducing the liver inflammation, steatosis and fibrosis compared to the positive control and also compared to 6-Ethyl CDCA (10 mpk/d) and Pioglitazone (10mpk/d) which were used as benchmark cpds. Thus, we believe that our new FXR agonists provide an excellent option as a new pharmacotherapy for the treatment of NASH

Stetic Animal model / Study Design:
C57Bl6 are injected with a single dose of Streptotoxin (STZ), three days after birth to destroy approx. 80% of all pancreatic β-cells.

At the age of 4 weeks animals are put on a high fat diet. This combined treatment results in the development of steatosis, hepatic insulin resistance, in particular, are considered as driving factors in the etiology of NASH, therefore any animal model that tries to resemble the human NASH situation has to take these factors into account. Currently, there is no dedicated treatment approved for NASH and due to the growing incidence of this disease in developed countries, there is also an increasing demand for a pharmaceutical that addresses the aforementioned factors. Stetic Institute & Co, has developed a novel murine model for NASH that closely mimics the human NASH situation in the sense that the animals display major hallmarks of human NASH including a moderate increase in transaminases and plasma lipids. The animals develop the entire cascade of metabolically induced liver disease from fatty liver / steatosis over NASH, to fibrosis, cirrhosis and ultimately hepatocellular carcinoma (HCC). Phenex AG has developed novel potent non-steroidal FXR agonists with a good pharmacokinetic profile that were tested in the Stetic mouse NASH model. We used three different administration regimes from five (5) to sixteen (16) weeks of administration to test for preventive as well as for curative effects. As an outcome, our new FXR agonists Px20350 and Px20606 show superior effects at doses of 10 and 30 mpk/d in reducing the liver inflammation, steatosis and fibrosis compared to the positive control and also compared to 6-Ethyl CDCA (10 mpk/d) and Pioglitazone (10mpk/d) which were used as benchmark cpds. Thus, we believe that our new FXR agonists provide an excellent option as a new pharmacotherapy for the treatment of NASH

We draw two major conclusions from our studies:
1) The Stetic mouse model seems to be very appropriate to test drugs for their anti-NASH effects because one can monitor steatosis, fibrosis and inflammation in a murine NASH model which closely resembles the human histopathology.
2) Our potent synthetic non-steroidal FXR agonists show superior anti-steatotic, anti-inflammatory and general hepatoprotective properties compared to Pioglitazone and 6-Ethyl CDCA as a PPARγ and a steroidal FXR agonist, respectively.

FXR agonists and other compounds used in this study

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