Obicetrapib alone and in combination with ezetimibe increases reverse cholesterol transport and does not affect VLDL production

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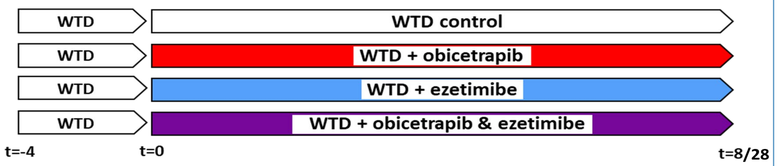
1. Background

Obicetrapib is a selective cholesteryl ester transfer protein (CETP) inhibitor that strongly reduces apolipoprotein B (apoB) and low-density lipoprotein cholesterol (LDL-C) and concomitantly increases high-density lipoprotein cholesterol (HDL-C) in humans. Combination of obicetrapib with ezetimibe, a selective inhibitor of biliary and dietary cholesterol absorption improves plasma lipids even further.

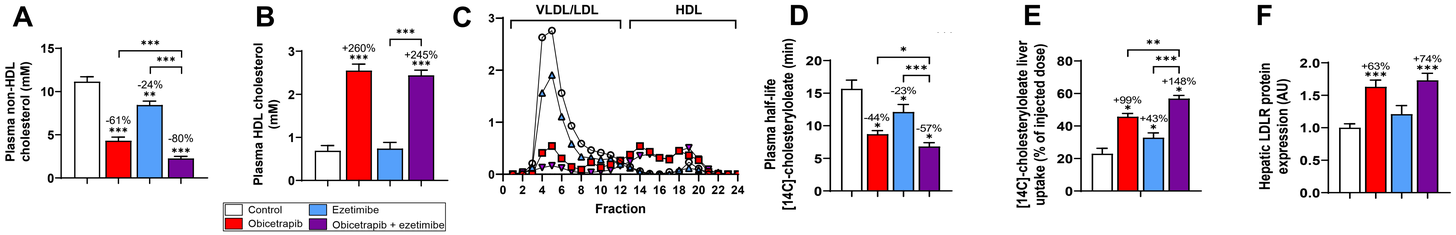
2. Study aims and design

Previously, we demonstrated that obicetrapib alone and with ezetimibe reduced non-HDL-C levels by increasing VLDL clearance and LDL receptor expression. To further elucidate the mechanism of action of obicetrapib and ezetimibe, VLDL production, intestinal absorption and reverse cholesterol transport (RCT) were measured. APOE*3-Leiden.CETP mice were used, a translational model with a human-like lipoprotein metabolism that develops hyperlipidemia when fed a Western-type diet (WTD). Mice were fed WTD with 0.05% cholesterol (equivalent to daily human intake). The diet was either given alone or supplemented with obicetrapib (2 mg/kg/day), ezetimibe (0.6-1 mg/kg/day) or both, aiming at similar non-HDL-C reductions as in humans.



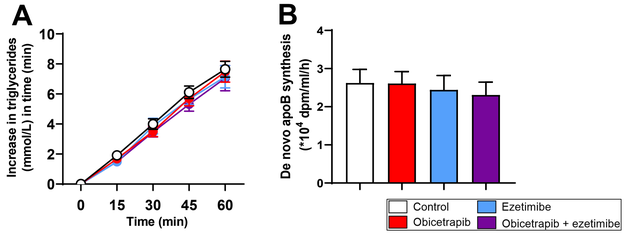
3.1 Obicetrapib alone and in combination with ezetimibe reduces non-HDL-C levels and increases VLDL clearance and hepatic LDLR expression in APOE*3-Leiden.CETP mice

Obicetrapib, ezetimibe and the combination reduce non-HDL-C levels **(A)**. Obicetrapib alone and in combination with ezetimibe nearly completely block CETP activity (not shown) resulting in increased HDL-C levels **(B)**. Evaluation of lipoprotein profiles reveals that mice treated with obicetrapib alone or in combination with ezetimibe hold their cholesterol minimally confined into (V)LDL particles but instead mainly into (large) HDL particles **(C)**. Obicetrapib, ezetimibe and to a larger extent their combination increase clearance of VLDL-like particles, resulting in a decreased half-life of VLDL-like particles **(D)** and increased liver uptake of VLDL-like particles **(E)**. Obicetrapib alone and in combination with ezetimibe enhances hepatic LDL receptor expression **(F)**.



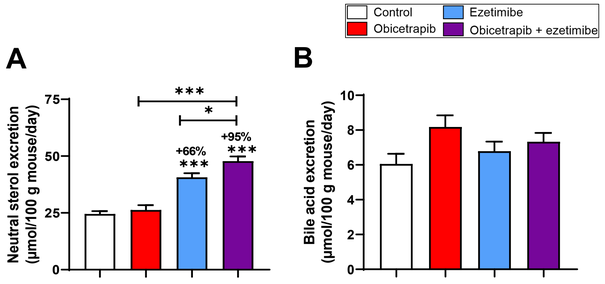
3.2 Obicetrapib and ezetimibe do not affect VLDL production

Lipolysis was blocked by intravenous Triton WR1339 injection. Obicetrapib, ezetimibe and the combination thereof did not affect VLDL-TG production (**A**) or *de novo* apoB synthesis (**B**).



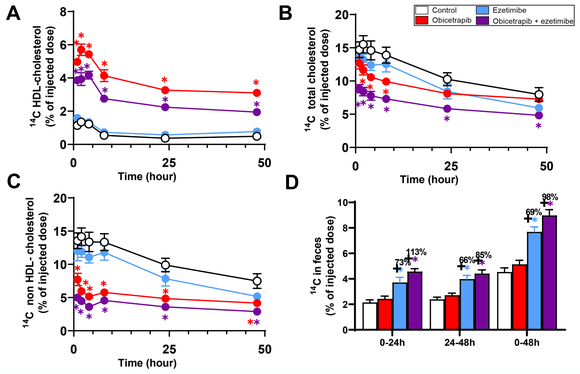
3.3 Obicetrapib with ezetimibe induces fecal neutral sterol excretion

Ezetimibe alone increased fecal neutral sterols and even more pronounced in combination with obicetrapib (**A**). Fecal bile acids were not affected (**B**).



3.4 Obicetrapib alone and in combination with ezetimibe increases reversed cholesterol transport (RCT)

After intravenous injection of ^{14}C-cholesterol nanoparticles, obicetrapib alone and in combination with ezetimibe increased RCT, as indicated by an increased reappearance of the ^{14}C-cholesterol label in HDL-C particles (**A**), a decreased reappearance of the ^{14}C-cholesterol label in total cholesterol (**B**) and non-HDL (**C**), and an increased excretion of the label in feces collected after 48 hours post-injection (**D**).



4. Conclusions

Obicetrapib alone and in combination with ezetimibe reduces non-HDL-C levels and increases VLDL clearance without affecting VLDL-TG production or *de novo* apoB synthesis. The combination of obicetrapib and ezetimibe induces net fecal sterol loss and increases reversed cholesterol transport with excretion in the feces.

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