Additive hepatoprotective effects of semaglutide and resmetirom combination therapy in the GAN diet-induced obese and biopsy-confirmed mouse model of MASH

Authors
Kristoffer Voldum-Clausen1, Jenny Norlin5, Line Wendt Nilsson1, Dennis Oul6, Gregoraz Macag1, Sanne Skogdørl Væda4, Henrik H. Hansen2, Michael Feighh2
1Guba, Harsholm, Denmark
2Novo Nordisk, Måld, Denmark

Background & Aim
Resmetirom (THR-β receptor agonist) has recently been approved for the treatment of metabolic dysfunction-associated steatohepatitis (MASH) and semaglutide (GLP-1R agonist) is in late-stage clinical development for treatment of MASH. The present study aimed to characterize metabolic, biochemical, histological, and transcriptomic outcomes of resmetirom and semaglutide combination treatment in the translational GAN diet-induced obese (DIO) and biopsy-confirmed mouse model of MASH with liver fibrosis.

Conclusions
• Semaglutide + Resmetirom combo treatment promote superior weight loss to mono treatments.
• Semaglutide + Resmetirom combo treatment improved hepatomegaly and plasma/lebera lipids superior to mono treatments.
• Semaglutide + Resmetirom combo treatment improved NAS (2-point) superior to mono treatments.
• Semaglutide + Resmetirom combo treatment reduces steatosis superior to mono treatments.
• Only resmetirom mono treatment reduces markers of fibrosis and improves fibrosis stage.
• Only resmetirom + semaglutide combo treatment amplified hepatic transcriptomic profile.

See the poster to download the poster.

Background & Aim
Resmetirom (THR-β receptor agonist) has recently been approved for the treatment of metabolic dysfunction-associated steatohepatitis (MASH) and semaglutide (GLP-1R agonist) is in late-stage clinical development for treatment of MASH. The present study aimed to characterize metabolic, biochemical, histological, and transcriptomic outcomes of resmetirom and semaglutide combination treatment in the translational GAN diet-induced obese (DIO) and biopsy-confirmed mouse model of MASH with liver fibrosis.

Conclusions
• Semaglutide + Resmetirom combo treatment promote superior weight loss to mono treatments.
• Semaglutide + Resmetirom combo treatment improved hepatomegaly and plasma/lebera lipids superior to mono treatments.
• Semaglutide + Resmetirom combo treatment improved NAS (2-point) superior to mono treatments.
• Semaglutide + Resmetirom combo treatment reduces steatosis superior to mono treatments.
• Only resmetirom mono treatment reduces markers of fibrosis and improves fibrosis stage.
• Only resmetirom + semaglutide combo treatment amplified hepatic transcriptomic profile.

See the poster to download the poster.

Figures and tables

Figure 1. Study outline. PO: per oral, SC: subcutaneous, GAN: generic fatty acid. GHOST deep learning image analysis (panels C, D, I). IHC image analysis (panels F). **p<0.01, ***p<0.001. Log2 Fold Change compared to vehicle. Figure 2. Semaglutide + Resmetirom combo treatment improved histological marker of steatosis superior to mono treatments.

Figure 3. Study outline. PO: per oral, SC: subcutaneous, GAN: generic fatty acid. GHOST deep learning image analysis (panels C, D, I). IHC image analysis (panels F). **p<0.01, ***p<0.001. Log2 Fold Change compared to vehicle. Figure 2. Semaglutide + Resmetirom combo treatment improved histological marker of steatosis superior to mono treatments.

Figure 4. Histological markers of steatosis, inflammation and fibrosis

Figure 5. NASH Activity Score and Fibrosis Stage

Figure 6. Hepatic transcriptomic profile

Figure 7. Semaglutide + Resmetirom combo treatment improved histological marker of steatosis superior to mono treatments.

Figure 8. Hepatic transcriptomic profile

Figure 9. Histological markers of steatosis, inflammation and fibrosis

Table 1. Study outline. PO: per oral, SC: subcutaneous, GAN: generic fatty acid. GHOST deep learning image analysis (panels C, D, I). IHC image analysis (panels F). **p<0.01, ***p<0.001. Log2 Fold Change compared to vehicle.