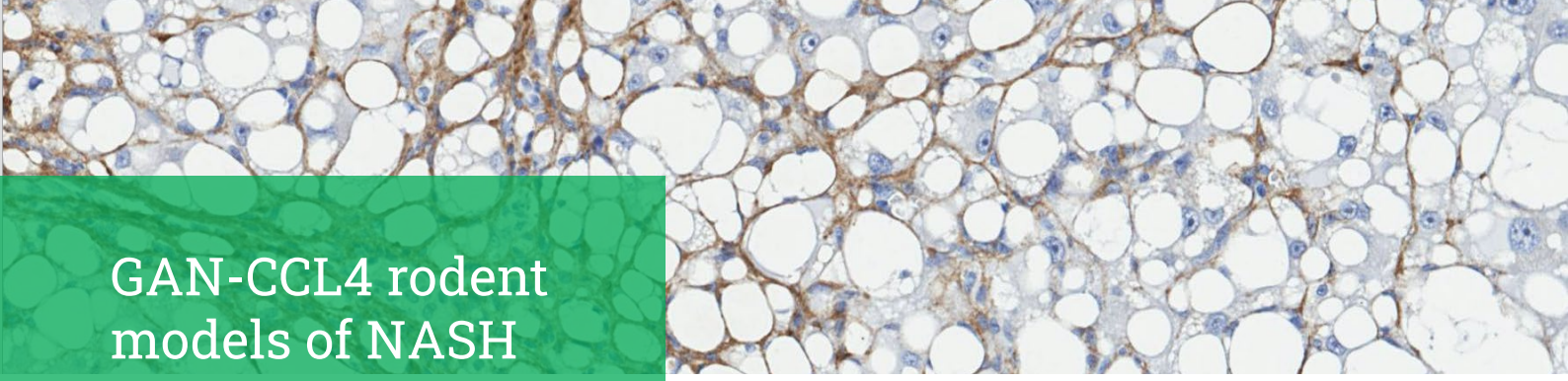


GAN-CCL4 rodent models of NASH

The GAN-CCL4 rodent models of advanced NASH with progressive fibrosis.

GAN-CCL4 mouse model

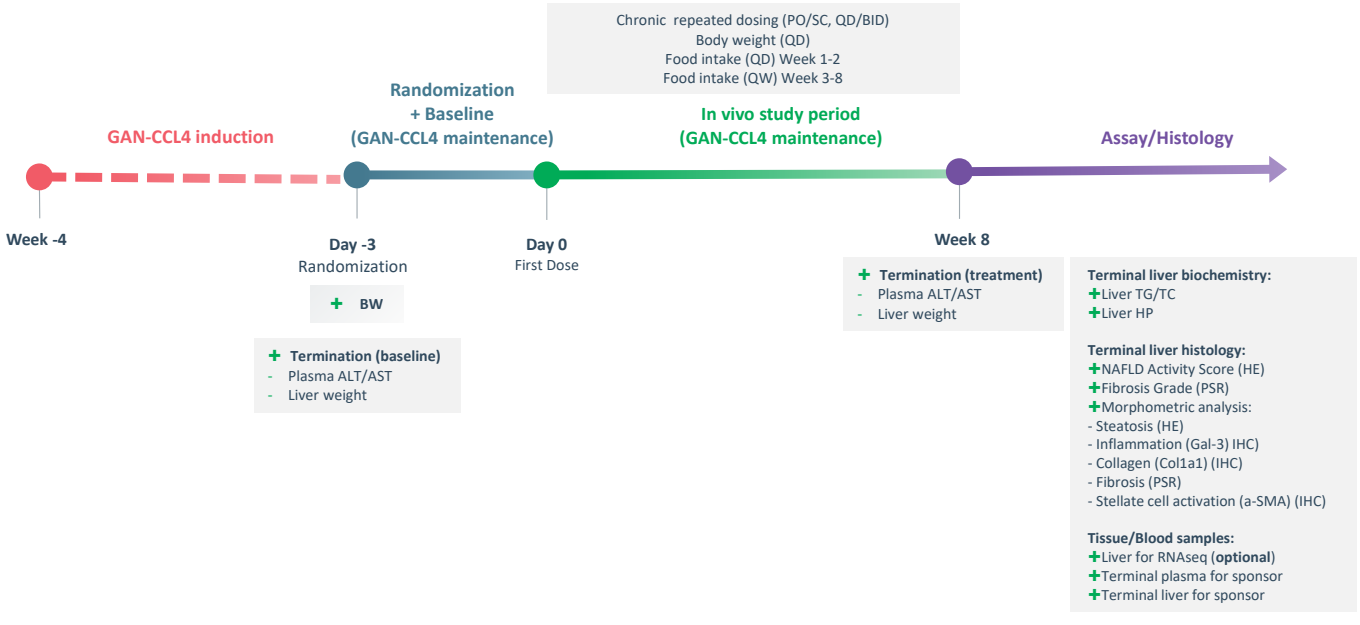
The GAN-CCL4 model is based on GAN diet-induction in combination with CCL4 for 4 weeks prior to study start. The GAN-CCL4 mouse exhibits non-metabolic associated advanced NASH and progressive fibrotic development, objectively evaluated by histopathological assessment including clinically-derived NAFLD Activity Score and Fibrosis Grade.

Key model traits

- GAN diet high in fat, fructose and cholesterol in combination with CCL4 for up to 12 weeks.
- Non-obesity without metabolic disease.
- Early onset of steatosis and fibrosis.
- Fast disease progression to advanced fibrosis and cirrhosis.
- Clinical histopathological endpoints.
- Prophylactic evaluation of drug efficacy.

Diet	40% fat (palm oil) 40% carbohydrates (20% fructose) 2% cholesterol	Gubra Amylin NASH (GAN) diet; 09100310 Research diets Mice or rats are dosed (IP, PO) twice weekly with carbon tetrachloride (CCl4, 0.25 ml/kg) during the GAN diet feeding period.
Strain	Male C57BL/6J mice	

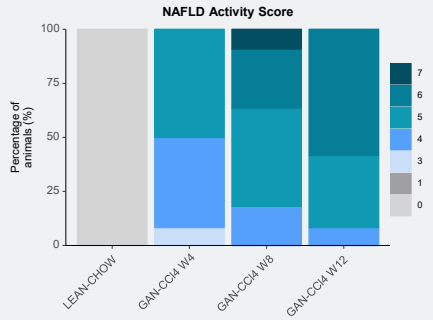
Study outline

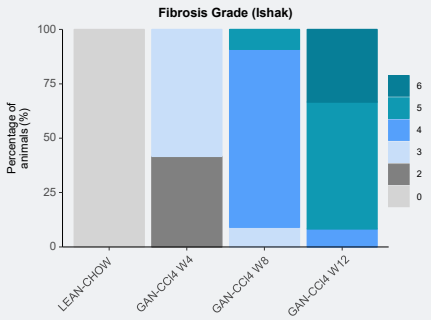


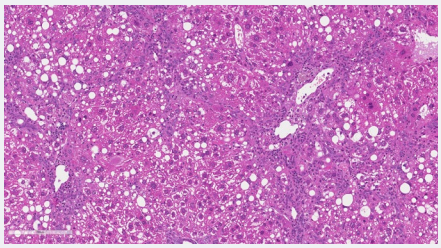
Metabolic, biochemical and histopathological profile

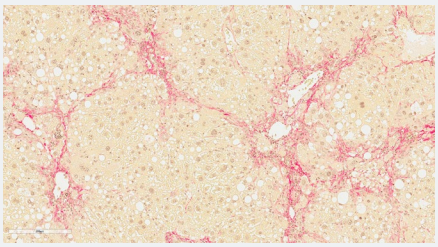
GAN-CCL4 mice are lean and show non-metabolic driven increases in hepatomegaly, steatosis, inflammation and fibrosis.

	CHOW	GAN-CCL4 W12
Body weight (g)	27.8 ± 0.85	25.4 ± 0.56
Liver weight (g)	1.12 ± 0.04	1.41 ± 0.04
Plasma ALT	19.8 ± 1.01	385 ± 32.2
Liver steatosis (HE) (% FA)	1.37 ± 0.04	11.2 ± 0.75
Liver inflammation (Gal-3) (% FA)	0.79 ± 0.04	10.4 ± 0.98
Liver fibrosis (PSR) (% FA)	0.41 ± 0.06	3 ± 0.21









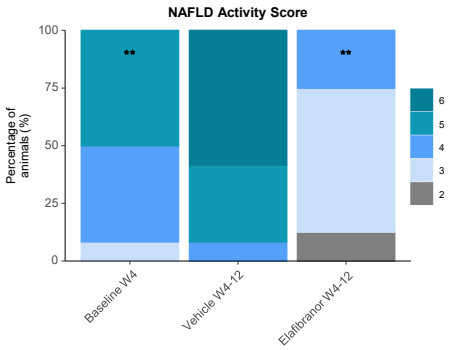
HE and PSR staining

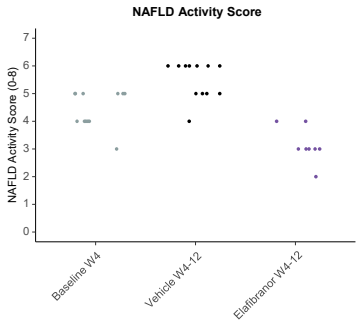
Clinical histopathological scores

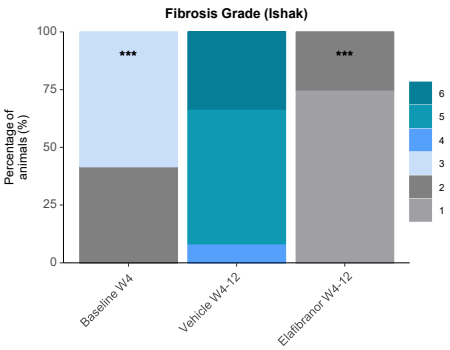
GAN-CCL4 mice show early disease onset and rapid progression of liver fibrosis, as determined using the clinically-derived NAFLD Activity Scoring and Fibrosis Grade (Kleiner, 2005; Ishak, 1995).

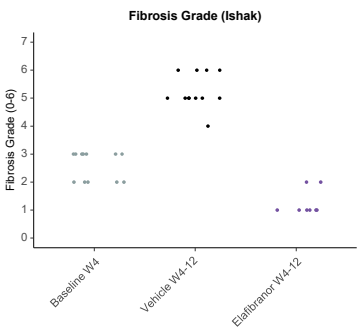
Histopathological NAFLD Activity Score and Fibrosis Grade

Assessment of NAFLD Activity Score and Fibrosis Grade allows for evaluation of individual treatment effects on liver histopathology. Effect of 8 weeks of treatment with the PPAR-α/d agonist Elafibranor.



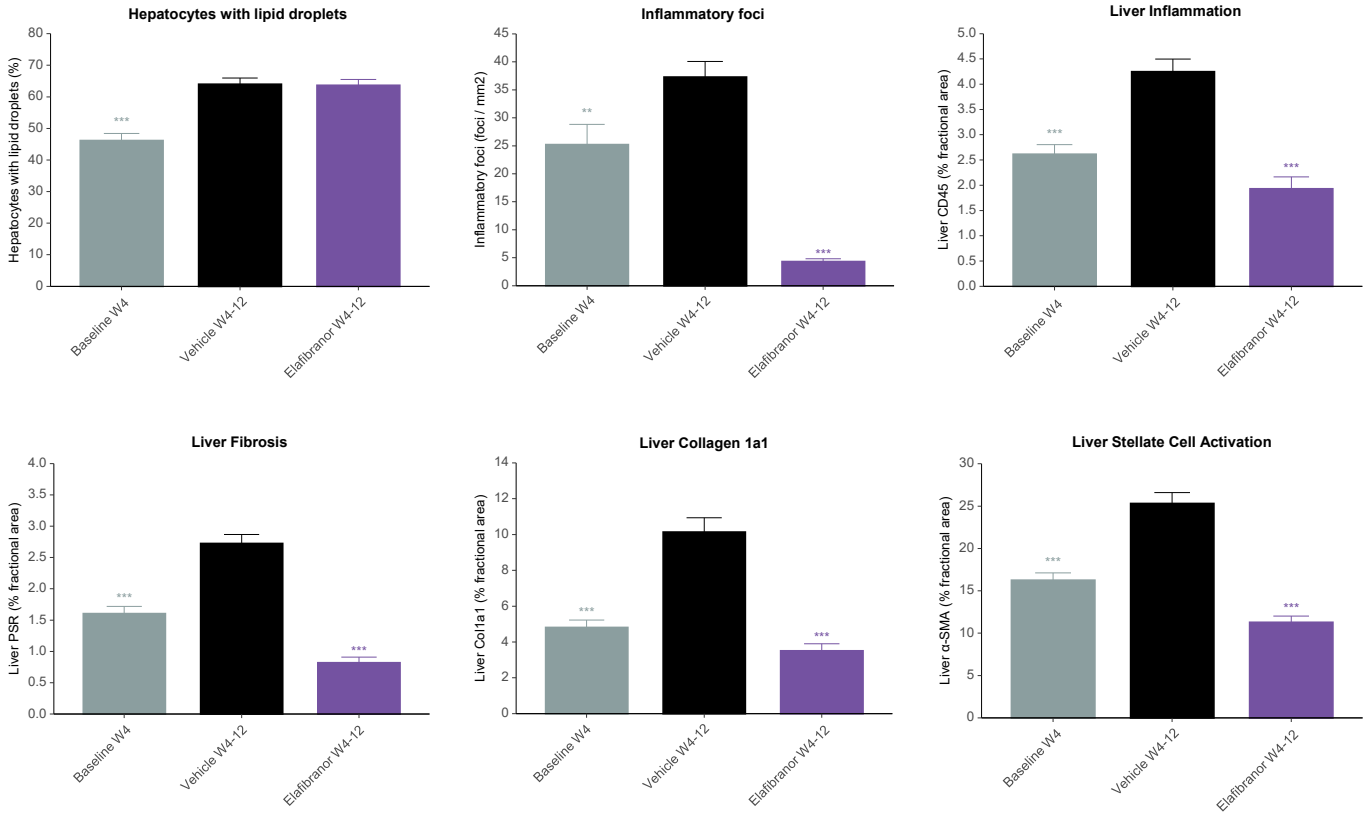






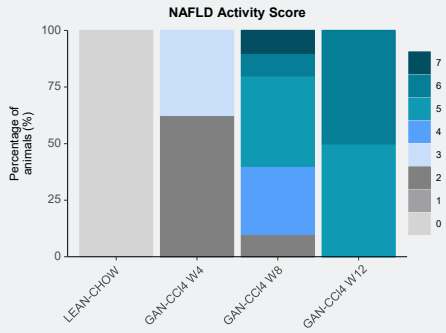
Histomorphometric evaluation of steatohepatitis and fibrosis

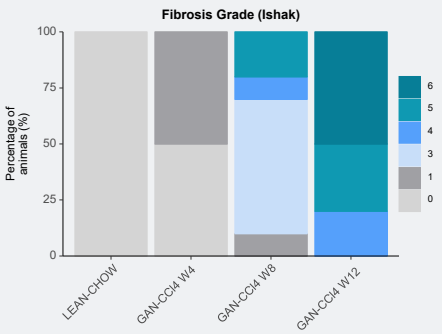
Quantitative assessment of liver steatosis, inflammation and fibrosis by histomorphometric image analysis. Effect of 8 weeks of treatment with the PPAR-α/d agonist Elafibranor.

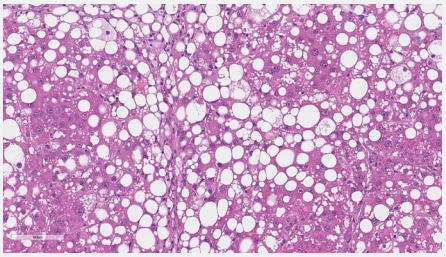


GAN-CCL4 rat model

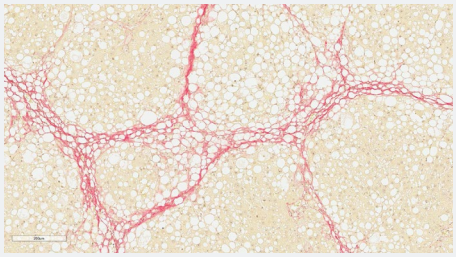
The GAN-CCL4 rat model is based on GAN diet-induction in combination with CCL4 for 4 weeks prior to study start. GAN-CCL4 rats exhibits non-metabolic associated moderate NASH and progressive fibrotic development, objectively evaluated by histopathological assessment including clinically-derived NAFLD Activity Score and Fibrosis Grade.

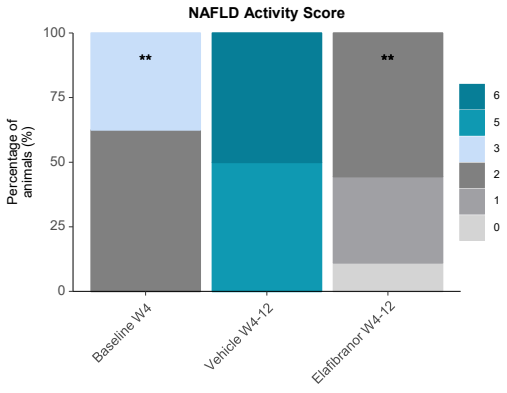


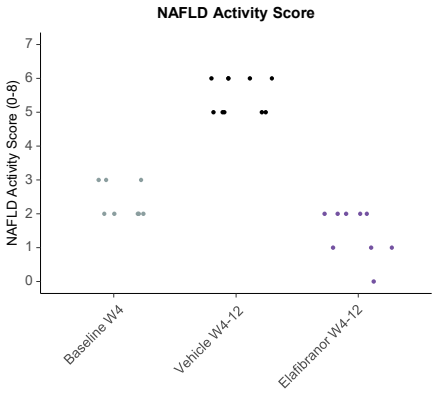


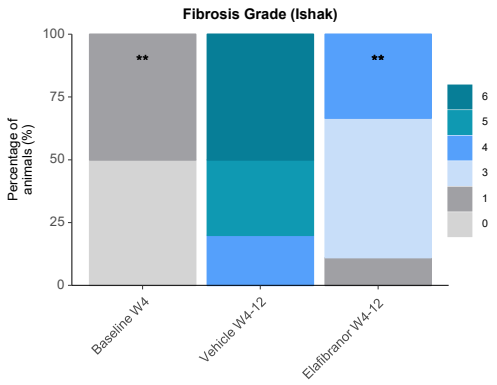


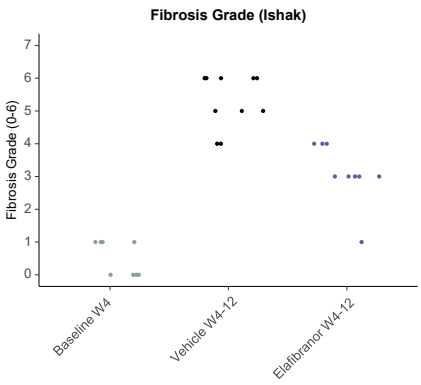
HE and PSR staining











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