CDAA-HFD rodent models of NASH

The CDAA-HFD rodent models of advanced NASH and progressive fibrosis.
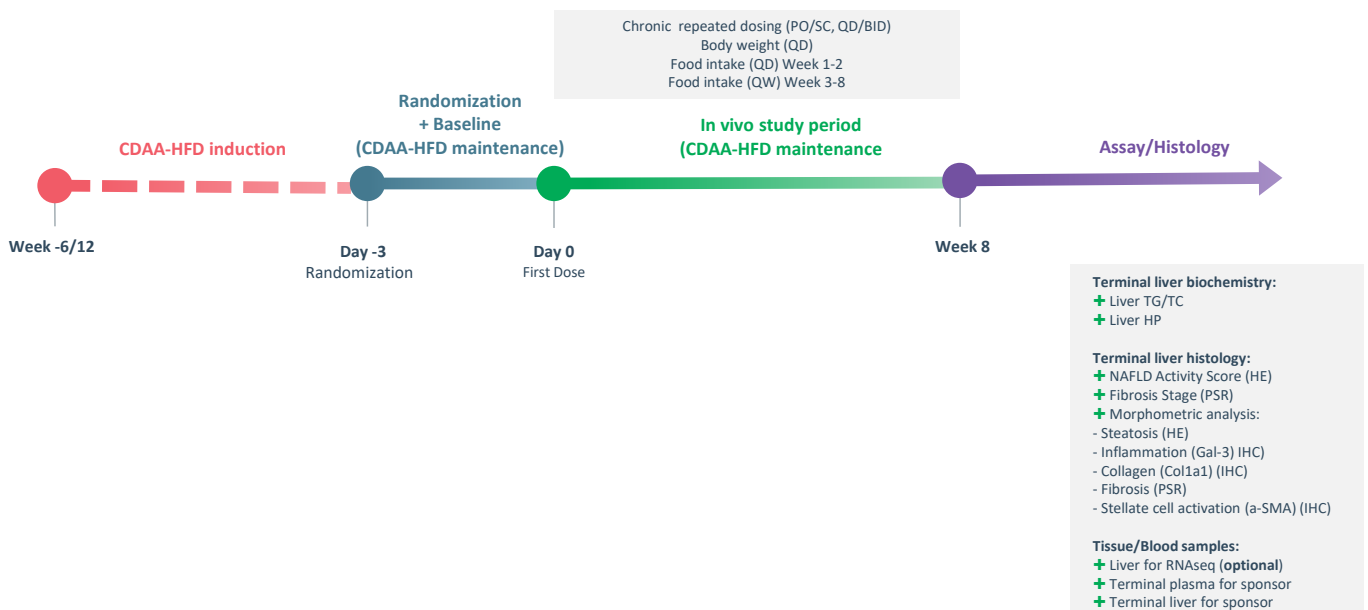
CCDA-HFD mouse model

The CDAA-HFD model is based on choline-deficient L-amino acid defined high fat diet (CDAA-HFD) induction for 6-12 weeks prior to study start. The CDAA-HFD mouse exhibits non-metabolic associated advanced NASH and progressive fibrotic development being objectively evaluated by histopathological assessment including NAFLD Activity Score and Fibrosis Stage.

Key model traits

- CDAA diet high in fat, fructose and cholesterol for up to 20 weeks.
- Non-obesity without metabolic disease.
- Early onset of steatosis and fibrosis.
- Fast disease progression to bridging fibrosis (stage F3).
- Clinical histopathological endpoints.
- Prophylactic and therapeutic drug efficacy.

|		
Diet	45% fat and 28% fructose 1% cholesterol, 0.1% methionine No choline	A16092201 Research diets Minimum 6 weeks on diet to develop hallmarks of fibrosing NASH
Strain	Male C57BL/6J mice	

Study outline

Chronic repeated dosing (PO/SC, QD/BID)
Body weight (QD)
Food intake (QD) Week 1-2
Food intake (QW) Week 3-8

CDAA-HFD induction

Randomization + Baseline (CDAA-HFD maintenance)

In vivo study period (CDAA-HFD maintenance

Assay/Histology

Week -6/12

Day -3
Randomization

Day 0
First Dose

Week 8

Terminal liver biochemistry:
+ Liver TG/TC
+ Liver HP

Terminal liver histology:
+ NAFLD Activity Score (HE)
+ Fibrosis Stage (PSR)
+ Morphometric analysis:
- Steatosis (HE)
- Inflammation (Gal-3) IHC)
- Collagen (Col1a1) (IHC)
- Fibrosis (PSR)
- Stellate cell activation (a-SMA) (IHC)

Tissue/Blood samples:
+ Liver for RNAseq (**optional**)
+ Terminal plasma for sponsor
+ Terminal liver for sponsor

## Metabolic, biochemical and histopathological profile

CDAA-HFD mice are lean and show non-metabolic driven increases in hepatomegaly, plasma liver enzymes, steatosis, inflammation and fibrosis.

	CHOW	CDAA-HFD (20w)
Body weight (g)	30.0 ± 0.4	24.1 ± 0.3
Liver weight (g)	1.3 ± 0.0	2 ± 0.1
Plasma ALT (U/L)	22 ± 1.5	301 ± 20
Liver steatosis (HE) (% FA)	1.02 ± 0.1	24.9 ± 0.8
Liver inflammation (Gal-3) (% FA)	1.44 ± 0.1	12.9 ± 0.3
Liver fibrosis (PSR) (% FA)	1.04 ± 0.1	8.76 ± 0.2
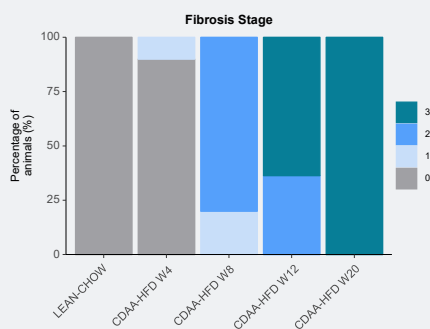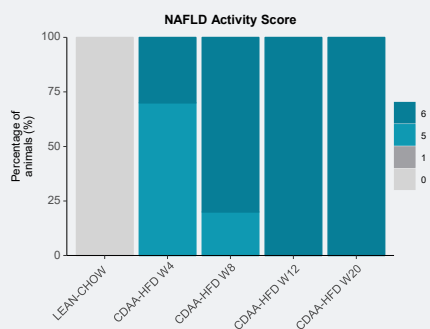
## Clinical histopathological scores

CDAA-HFD mice show early disease onset and fast progression of liver fibrosis, as determined using the clinical-derived NAFLD Activity Scoring and Fibrosis staging system (Kleiner, 2005).
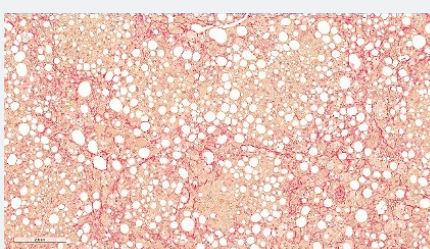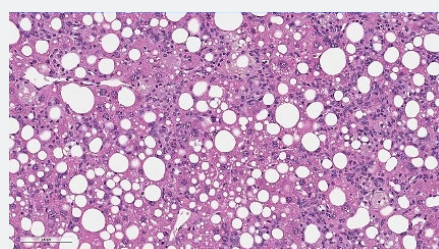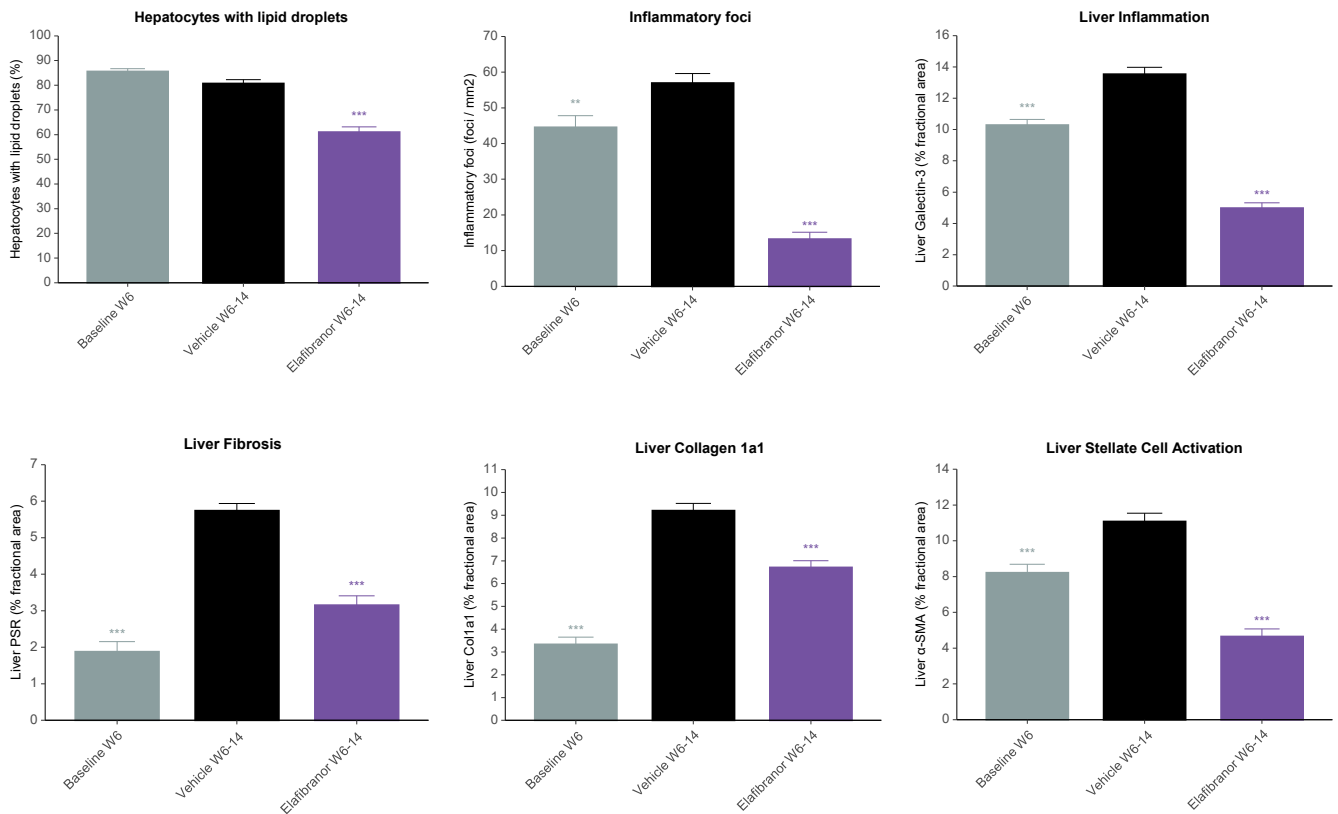
HE and PSR staining

Histopathological NAFLD Activity Score and Fibrosis Stage

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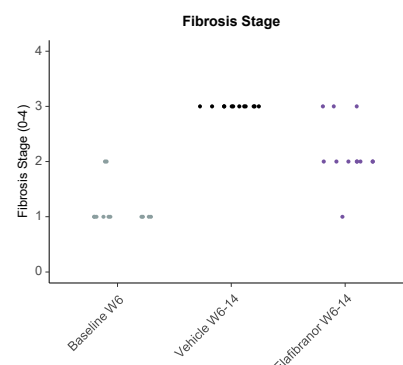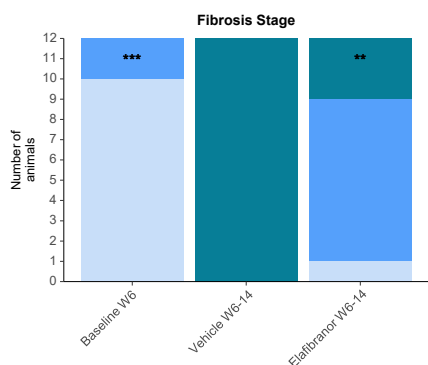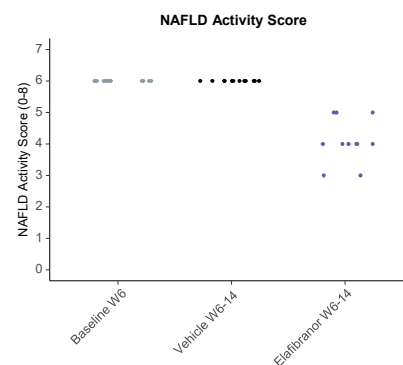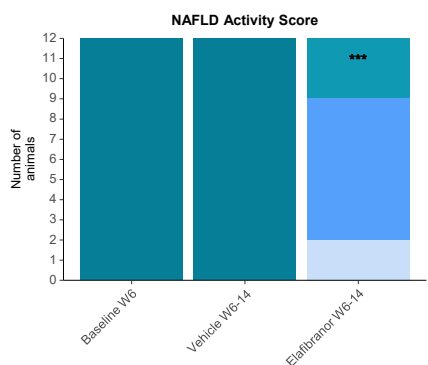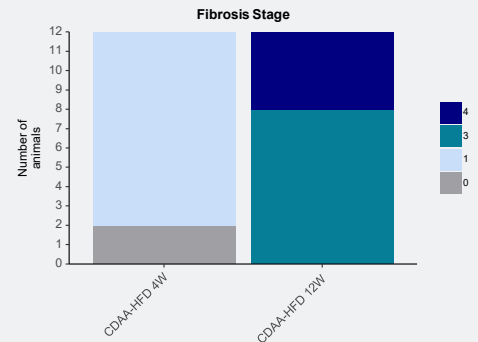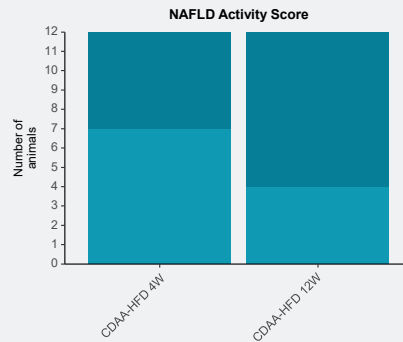
Histomorphometric evaluation of steatohepatitis and fibrosis

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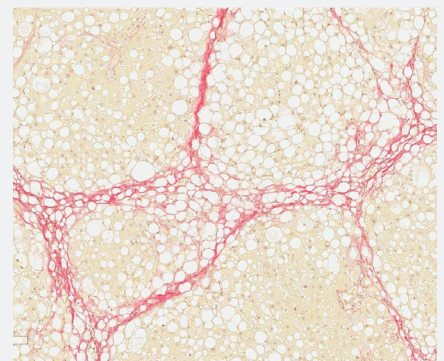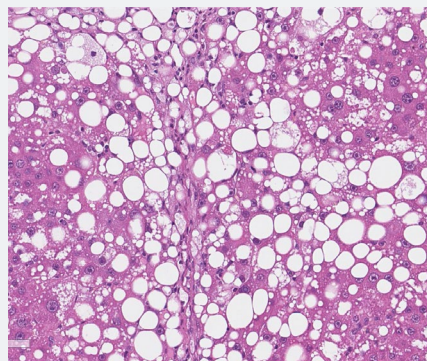

CDAA-HFD rat model

The CDAA-HFD rat model is based on choline-deficient L-amino acid defined high fat diet (CDAA-HFD) induction for 4-6 weeks prior to study start. CDAA-HFD rats are lean and show non-metabolic driven early disease onset and fast progression to advanced NASH with fibrosis and cirrhosis, as evaluated by clinical-derived NAFLD Activity Score and Fibrosis Stage.
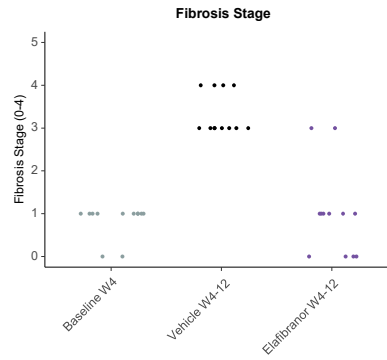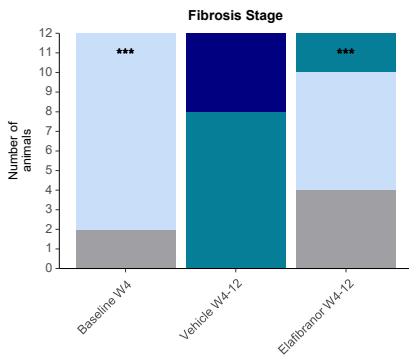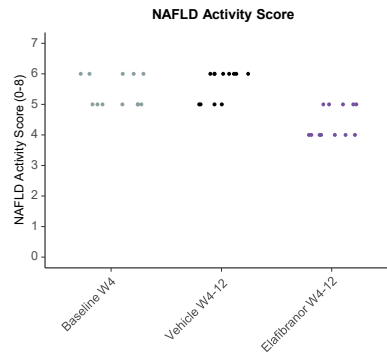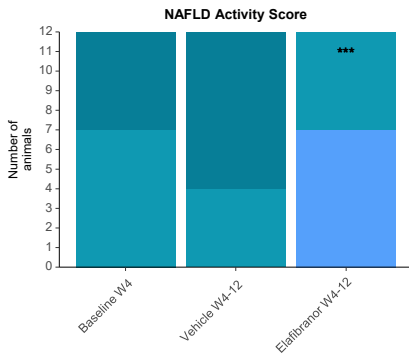

HE and PSR staining

NAFLD Activity Score

Fibrosis Stage

Histopathological NAFLD Activity Score and Fibrosis Stage

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

Liver Steatosis

Liver Inflammation

Liver Collagen 1a1

Liver Stellate Cell Activation