Reliable and Reproducible Preclinical Rodent Models of MASH

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Background & Objective

Metabolic dysfunction-associated steatohepatitis (MASH) leading to hepatocellular carcinoma (HCC). Here, at Aragen, our scientists have established therapeutic intervention with Elafibranor in three different murine models of MASH compiling the different dietary compositions, Choline-deficient, L-amino acid-defined, high-fat diet (CDAA-HFD), High-fat, high-fructose, high-cholesterol (FFC; Western diet (WD)) + CCl4 diet and High-fat, high-fructose, high-cholesterol (FFC) diet and evaluated their impact on metabolic, biochemical and histological outcomes. Elafibranor tested across the different models has reproducibly shown metabolic, biochemical and histological improvements. At Aragen, our extensive experience within the MASH and fibrosis field gives us the expertise for execution of reproducible and successful preclinical studies.

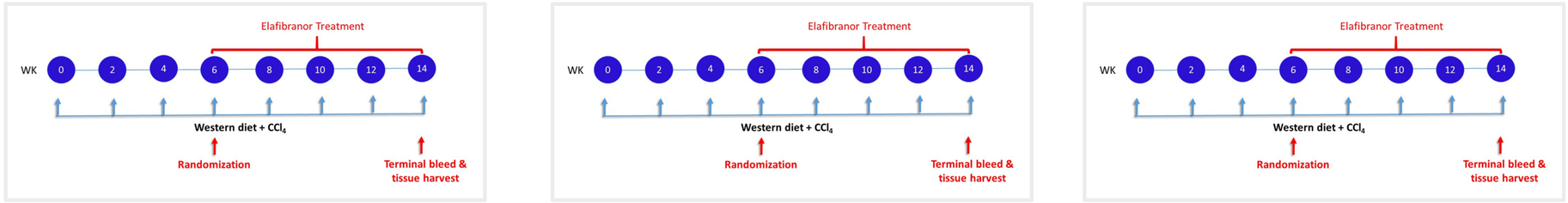
Creation of Customized, Client-Specific Study Designs in Mouse Model for MASH

- **Study animals:** Male C57BL/6 (aged 6-8 weeks)
- **Disease induction:** CDAA-HFD, FFC-HFD or WD + CCl4
- **Option of test article administration:** PO, IP, IV, IM, SC and inhalation
- **Treatment regimen:** Therapeutic or Prophylactic
- **Positive reference:** Elafibranor (30 mg/kg, QD)

Summary & Conclusions

Evaluation of new drugs, either small molecule or biologics, requires robust and reliable pre-clinical animal models. Aragen Bioscience offers customized and high quality pre-clinical animal models with multiple readouts to support your anti-fibrotic drug development. Our expert and experienced staff provide scientific input and support for all project stages. Visit our website at www.aragenbio.com and have Aragen be your partner for characterization and development of new drugs for this important medical need.

1 Study Design: (A) Western Diet + Ccl^4 (B) CDAA-HFD Model (C) FFC-HFD (Amylin) Model



2 Metabolic & Biochemical Parameters

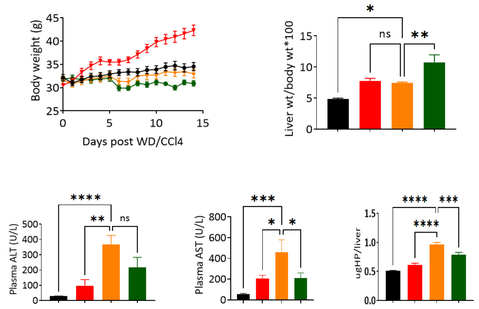


Figure 1: Effect of therapeutic Elafibranor treatment on body weight (A), liver/bw index (B), plasma levels of ALT (C), AST (D) and liver hydroxyproline (E) in WD/CCl4 mice. Ref: Tsuchida et al, 2018: J Hepatology.

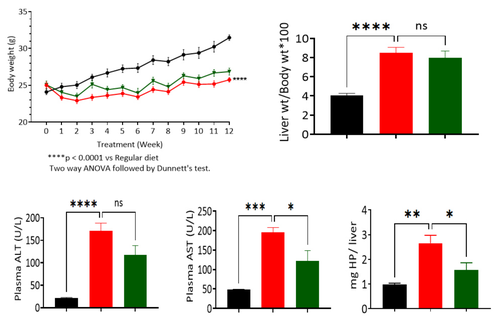


Figure 2: Effect of therapeutic Elafibranor treatment on body weight (A), liver/bw index (B), plasma levels of ALT (C) AST (D) and liver hydroxyproline (E) in CDAA-HFD fed mice. Ref: Matsumoto et al, 2013: Int J Expt Pathology.

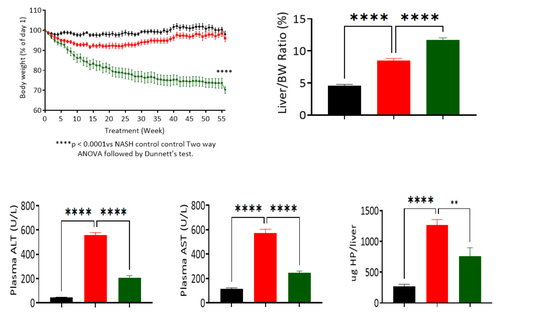


Figure 3: Effect of therapeutic Elafibranor treatment on body weight (A), liver/bw index (B), plasma levels of ALT (C), AST (D) and liver hydroxyproline (E) in FCC-HFD (Amylin) fed mice. Ref: Honda et al., 2016: Plos One.

3 NAS Score (H&E), Steatosis (ORO) & Fibrosis (PSR)

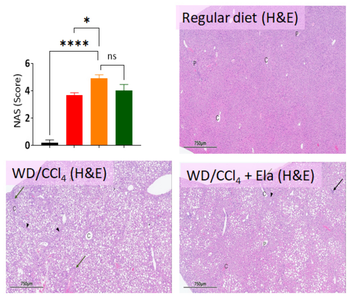


Figure 4: Effect of therapeutic Elafibranor treatment on NAFLD Activity Score in WD/CCl4 fed mice. (A) NAFLD Activity Score (NAS). Representative H&E photomicrographs.

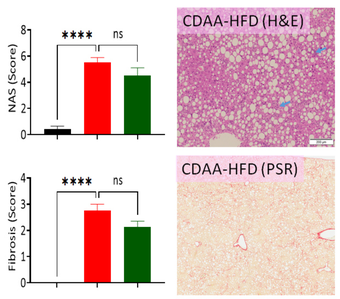


Figure 5: Therapeutic treatment effect of Elafibranor on NAFLD Activity Score and liver fibrosis in CDAA-HFD fed mice. (A) NAFLD Activity Score (NAS). **(B) Fibrosis score (PSR staining)** Right panels: Representative H&E and PSR photomicrographs.

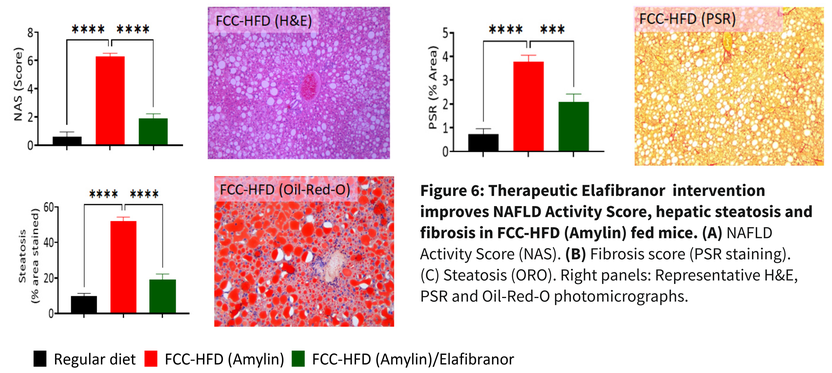


Figure 6: Therapeutic Elafibranor intervention improves NAFLD Activity Score, hepatic steatosis and fibrosis in FCC-HFD (Amylin) fed mice. (A) NAFLD Activity Score (NAS). **(B)** Fibrosis score (PSR staining). (C) Steatosis (ORO). Right panels: Representative H&E, PSR and Oil-Red-O photomicrographs.

4 Fibropanel™ Gene Expression Analysis