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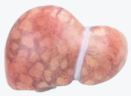
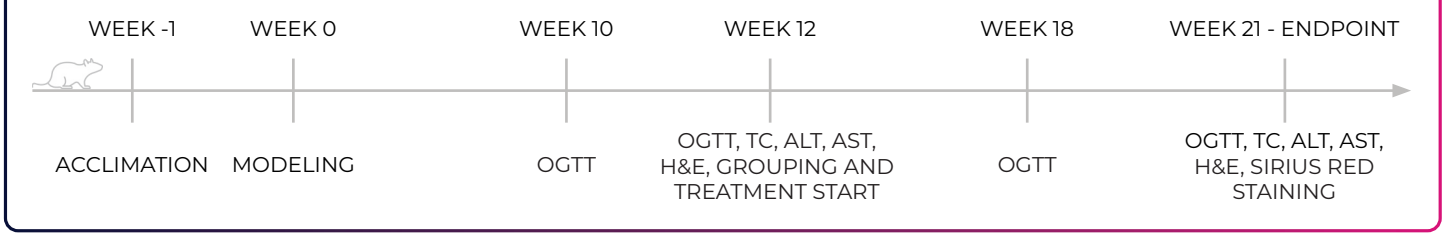
GUBRA AMYLIN NASH (GAN) DIET-INDUCED NASH MOUSE MODEL

- NAFLD is the hepatic manifestation of a number of conditions associated with metabolic dysfunction and is characterized by the accumulation of fat in the liver.
- Global prevalence of NAFLD sits at ~25% with global NASH prevalence at ~5%.
- Mechanisms leading to development and progression of NAFLD are complex and multifactorial; poor dietary habits, sedentary lifestyle, environmental factors, genetic factors
- Treatment options for NASH can be divided into the following categories; carbohydrate and lipid metabolism, inflammation-based, lipotoxicity and cell death, anti-fibrosis-based targeting ECM deposition

NORMAL LIVER	NAFL: NONALCOHOLIC FATTY LIVER	NASH: NONALCOHOLIC STEATOHEPATITIS	NASH: WITH FIBROSIS	CIRRHOSIS
				
Fat accumulation	Isolated steatosis (fat in ≥5% of hepatocytes)	• Steatosis • Ballooning • Inflammation	MILD • F1: fibrosis stage 1 MODERATE TO ADVANCED • F2: fibrosis stage 2 • F3: fibrosis stage 3	MILD • F4: fibrosis stage 4

GAN DIET-INDUCED NASH PRECLINICAL *IN VIVO* MOUSE MODEL



- Mice
  - Male C57BL/6, 6-8 weeks on arrival
- Diet
  - GAN diet (40 kcal% fat, 20 kcal% fructose, 2% cholesterol) – diet fed weeks 0-21
- Randomization
  - Mice grouped based on Week 12 ALT and AST levels

MAJOR READOUTS

- Body weight
- Liver/body weight ratio
- Glucose tolerance test
- Blood: AST, ALT and TC
- Pathology: H&E and Sirius Red staining
- NAFLD activity score (NAS)

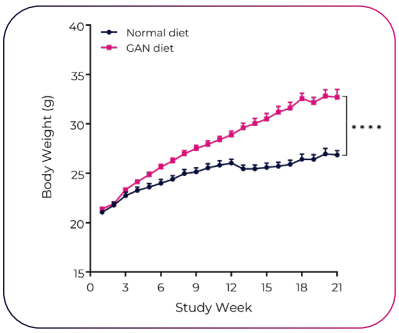
GAN DIET-INDUCED NASH MOUSE MODEL

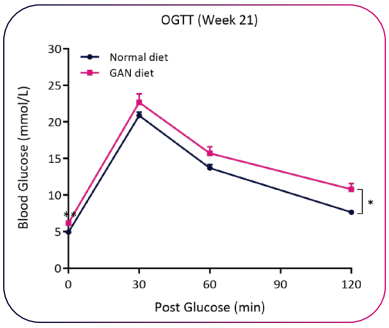
METABOLIC PHENOTYPE

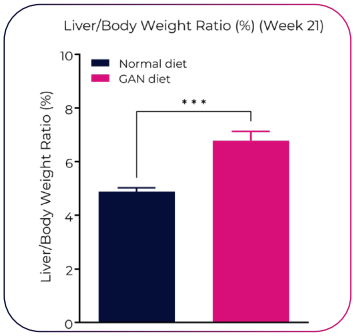
CLINICALLY RELEVANT

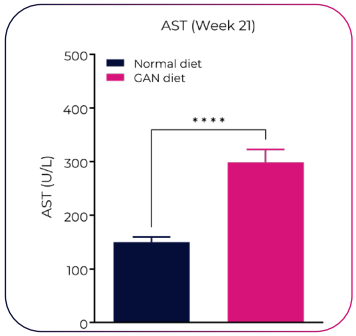
Animals are:

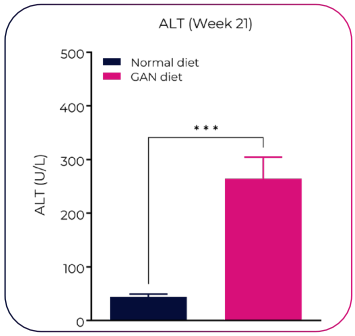
- ✓ Obese
- ✓ Glucose intolerant
- ✓ Secreting plasma markers of liver injury
- ✓ Exhibit a metabolic NAFLD/NASH phenotype
- ✓ Hypercholesterolemic

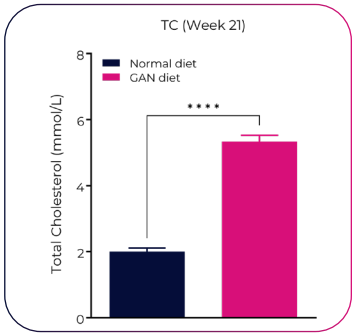






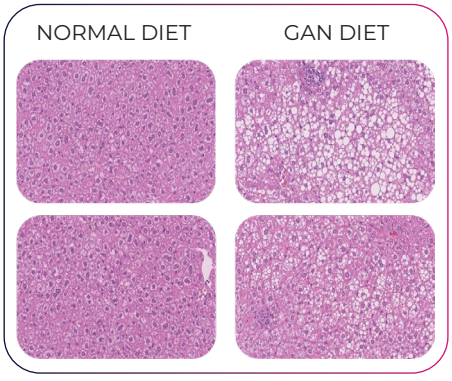


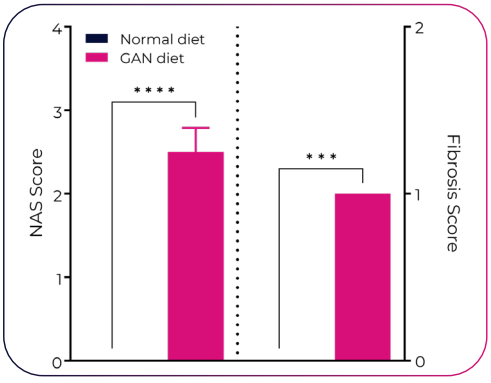


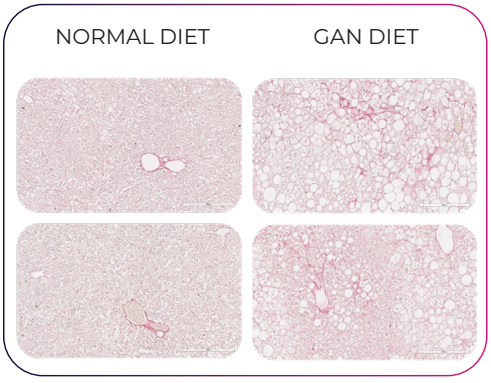


HISTOPATHOLOGICAL HALLMARKS OF GAN-NASH C57BL/6 MICE

- Statistically significant higher NAS score (p<0.0001) in mice fed on a GAN diet
- H&E staining revealed increased steatosis and lobular inflammation in GAN diet-induced mice
- Sirius Red staining of mouse liver revealed increased fibrosis (and the associated fibrosis score) in mice fed on a GAN diet (p=0.0001)
- Phenotype resembling human NASH-fibrosis







SUMMARY

The GAN-NASH mouse model is a cost-effective and clinically relevant model for assessing the therapeutic efficacy of new treatments for non-alcoholic steatohepatitis. By week 12 of modeling on the GAN diet, mice exhibit the metabolic and histopathological phenotypes of human NASH.

✓ Short induction period ✓ Cost effective ✓ Clinically relevant

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