



**EDP-305, a highly selective and potent FXR  
agonist, reduces liver steatosis, ballooning,  
and non-alcoholic fatty liver disease  
activity score(NAS) in two murine models  
of NASH**

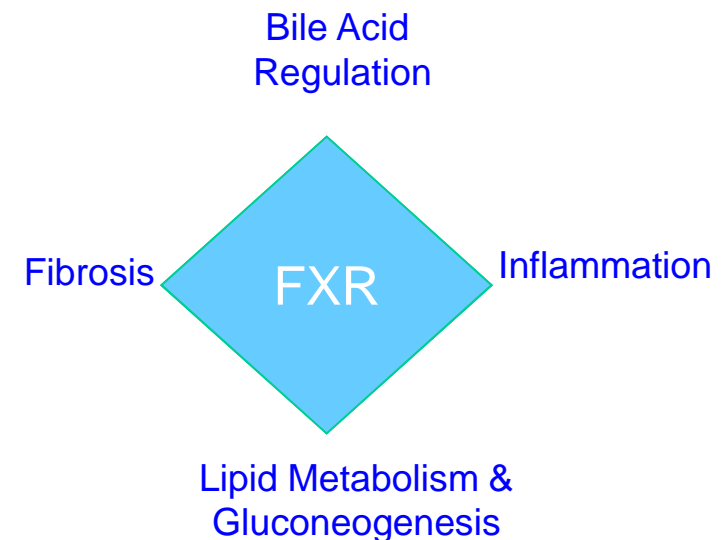
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# FXR has emerged as an attractive target for the treatment of NASH & PBC

- Clinical validation has been achieved in NASH and PBC with the FXR agonist obeticholic acid (OCA)
- FXR is a nuclear receptor and main regulator of bile acid levels in the liver and small intestine
- FXR responds to bile acids by regulating transcription of key enzymes and transporters
- FXR agonists have ameliorated a number of the pathologies in NASH, including effects on fibrosis, inflammation, lipid metabolism & gluconeogenesis

NASH = nonalcoholic steatohepatitis;  
PBC = primary biliary cholangitis

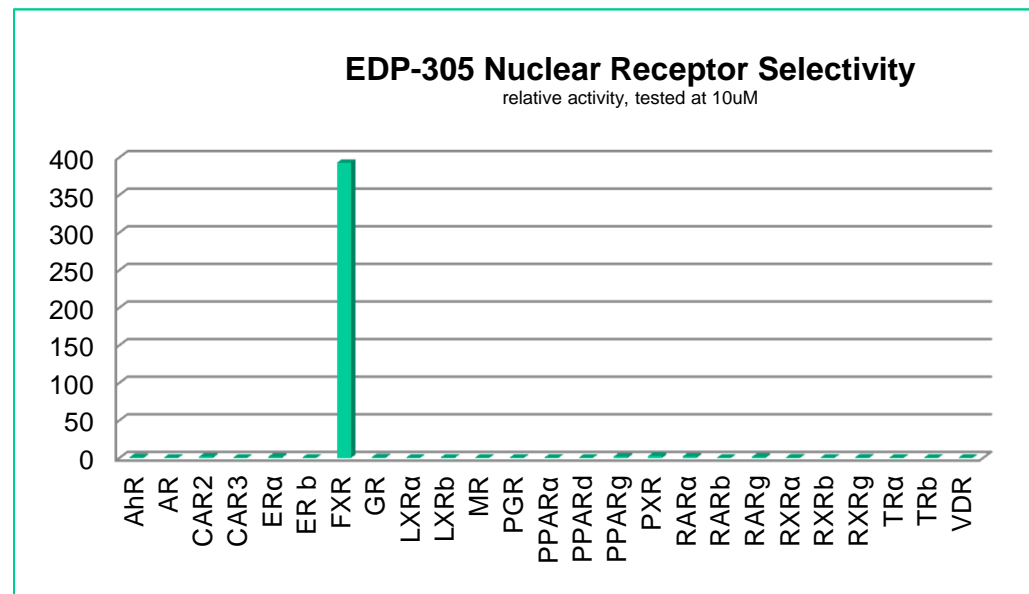
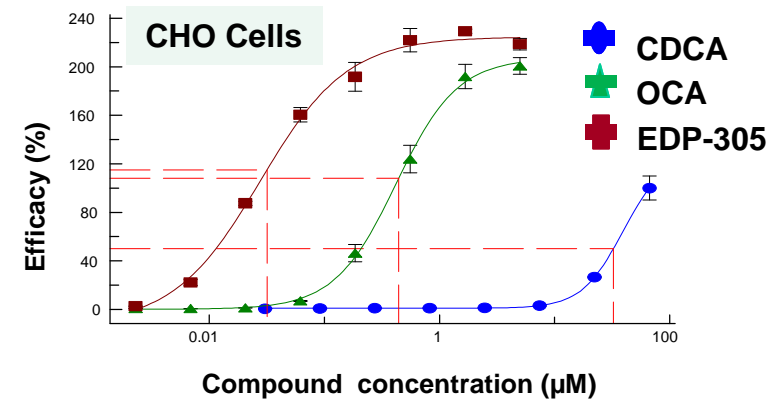


# EDP-305 is a potent and selective FXR agonist

## EDP-305 is >16-fold more potent than OCA and its major metabolites

Compound	FXR (HEK)	TGR5 (CHO)
	EC50 nM (% efficacy)*	
Obeticholic Acid (OCA)	130 (150)	380 (72)
Glyco-OCA	360 (155)	720 (157)
Tauro-OCA	250 (100)	540 (161)
<b>EDP-305</b>	<b>8 (152)</b>	<b>&gt; 15,000 (NS)</b>

\* Transporter inserted, FXR efficacy CDCA = 100%; TGR5 efficacy LCA = 100%



Y. Li, *et al*, AASLD 2016 poster 1540

# EDP-305 regulates key gene expression

*In vitro*

- **Bile acid metabolism**

- SHP; FGF19; OST- $\alpha$ ; BSEP; CYP7A1



- **Lipid metabolism**

- LDLR; PCSK9; SREBP-1C; SCD1; CD36; DGAT2; APOB; APOC3; HL; SRB1

- **Inflammation**

- NF- $\kappa$ B; TLR2; TLR9; TNF $\alpha$ ; IL8; IL1 $\alpha$ ; IL1 $\beta$ ; IL1R1; CCL2; CCR1; CCR4; CEBPB

- **Fibrosis**

- $\alpha$ -SMA; TIMP1; TIMP2; PDGF $\alpha$ ; PDGF $\beta$ ; COL1A2; COL3A1; ITGB6

- **Glucose metabolism**

- FGF21; IRS2; GLUT2; GLUT4; FOXO1

# EDP-305 exhibits its efficacy in eight (8) different animal models

- Mouse model
  - FXR mechanism of action: SHP, CYP7A1 and FGF15 (Enanta Pharmaceuticals, Inc.)
- Liver fibrosis/cirrhosis model
  - Thioacetamide-induced rat liver fibrosis/cirrhosis model (Icahn School of Medicine at Mt. Sinai)
- Biliary fibrosis models
  - Mdr2<sup>-/-</sup> mouse biliary fibrosis model (Harvard/BIDMC)
  - Rat bile duct ligation model (Harvard/MGH)
- NASH models
  - MCD-fed mouse steatohepatitis model with progressive fibrosis (Harvard/BIDMC)
  - Choline-deficient, L-amino acid-defined, high-fat-diet, mouse NASH model (Harvard/MGH)
  - STAM<sup>TM</sup> mouse NASH model (Stelic, Japan)
  - Diet-induced NASH(DIN) mouse model (Physiogenex, France)

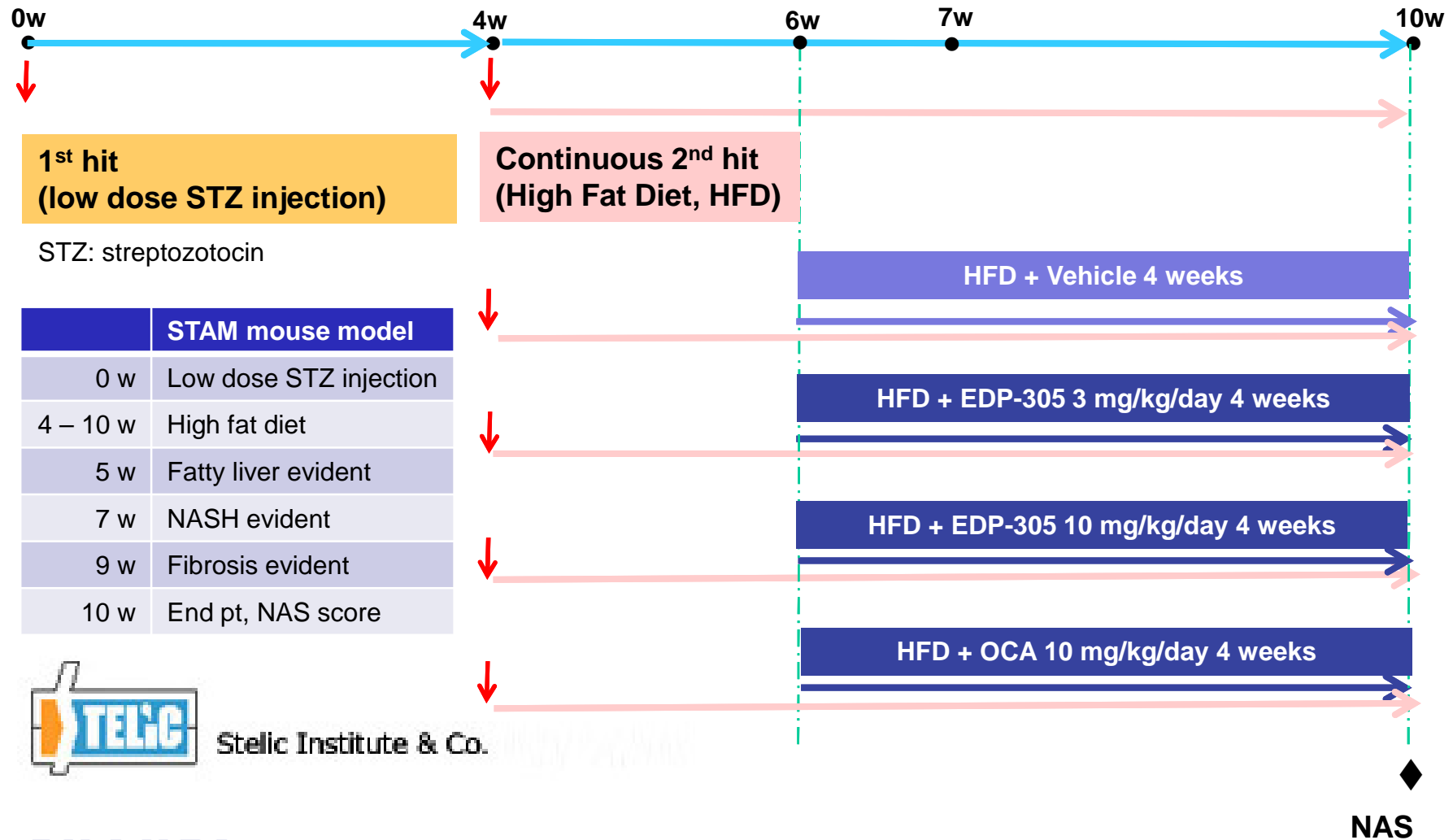
## EDP-305 protects rats and mice from liver steatosis and injury

- Lowers liver and plasma lipid contents (including cholesterol, TG & FFA)
- Reduces ballooning & fibrosis progression, and reduces inflammation
- Lowers NAFLD Activity Score (NAS)



# STAM™ NASH Mouse Model

# STAM™ mouse model

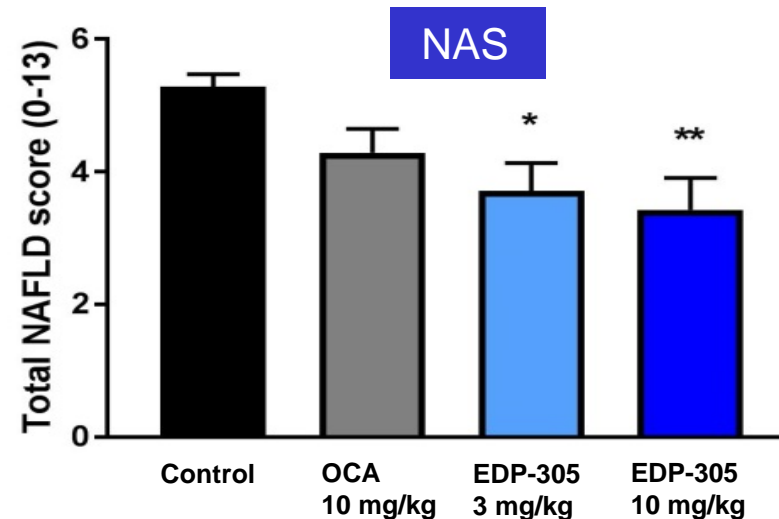
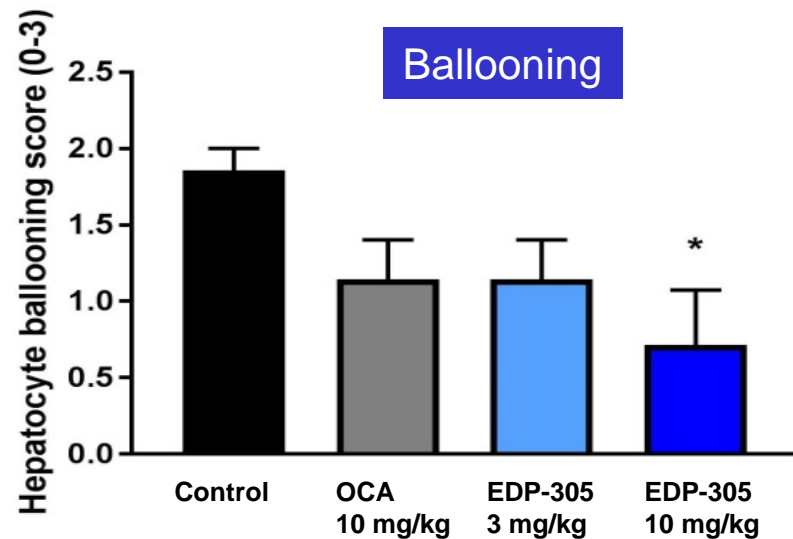


# EDP-305 vs OCA in STAM™ mouse model

## Non-alcoholic fatty liver disease activity score (NAS)

Drug	mg/kg/d	n	Hepatocyte Ballooning Score	NAS
Control	--	7	1.9	5.3
OCA	10	7	1.1	4.3
EDP-305	3	7	1.1	3.7*
EDP-305	10	7	0.7*	3.4**

\* p<0.05; \*\* p<0.01

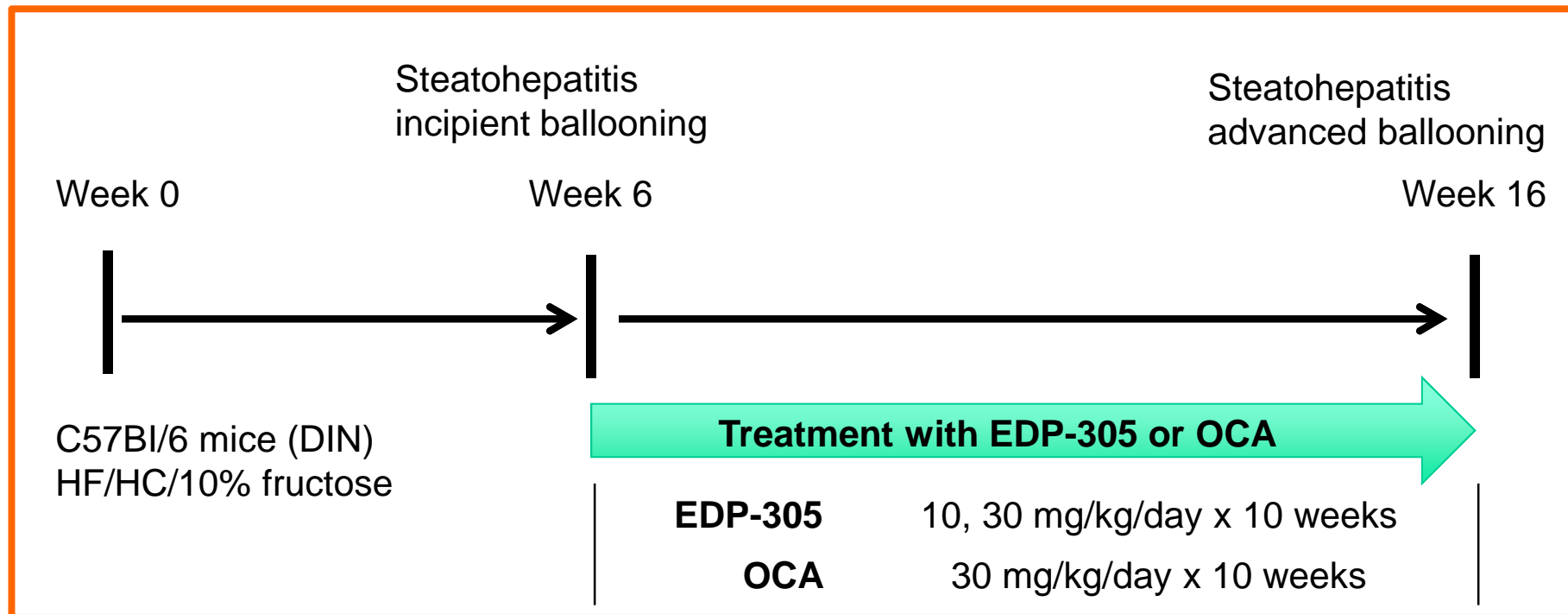






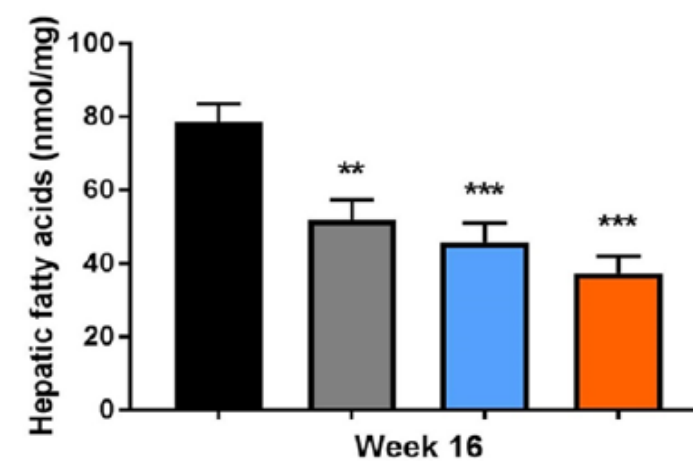
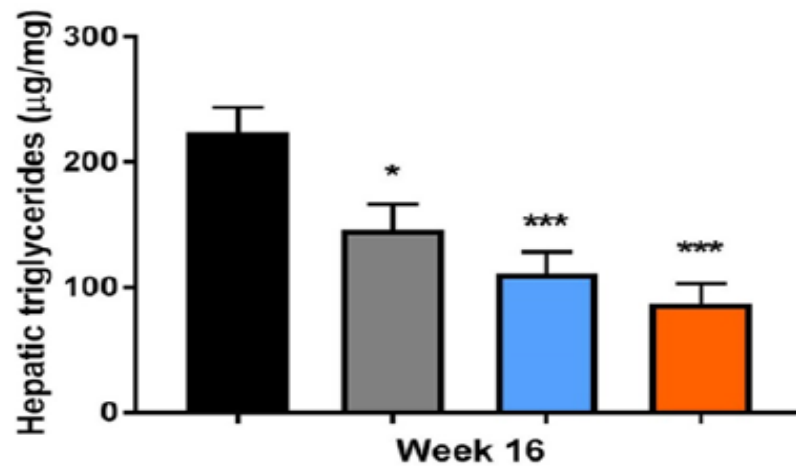
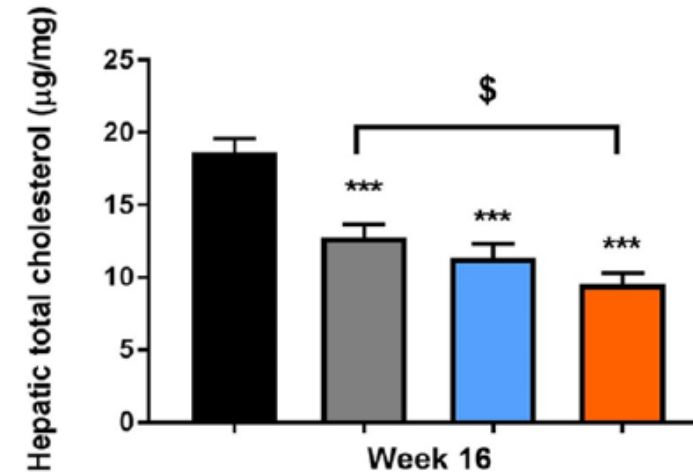
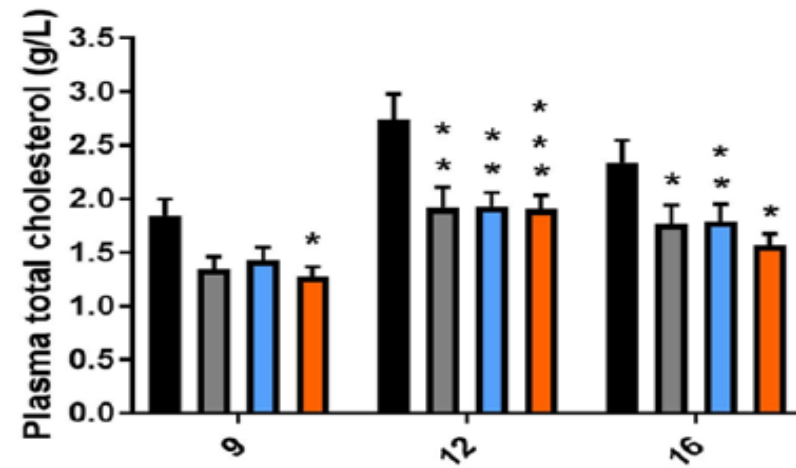
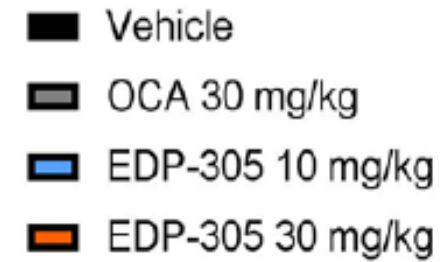
# Diet-induced NASH (DIN) Mouse Model

# EDP-305 decreases liver steatosis, ballooning, & NAS in a diet-induced NASH (DIN) murine model



EDP-305 significantly decreased liver steatosis, hepatocyte ballooning, and total NAS in diet-induced NASH (DIN) mice model.

# EDP-305 reduces plasma and liver lipid contents

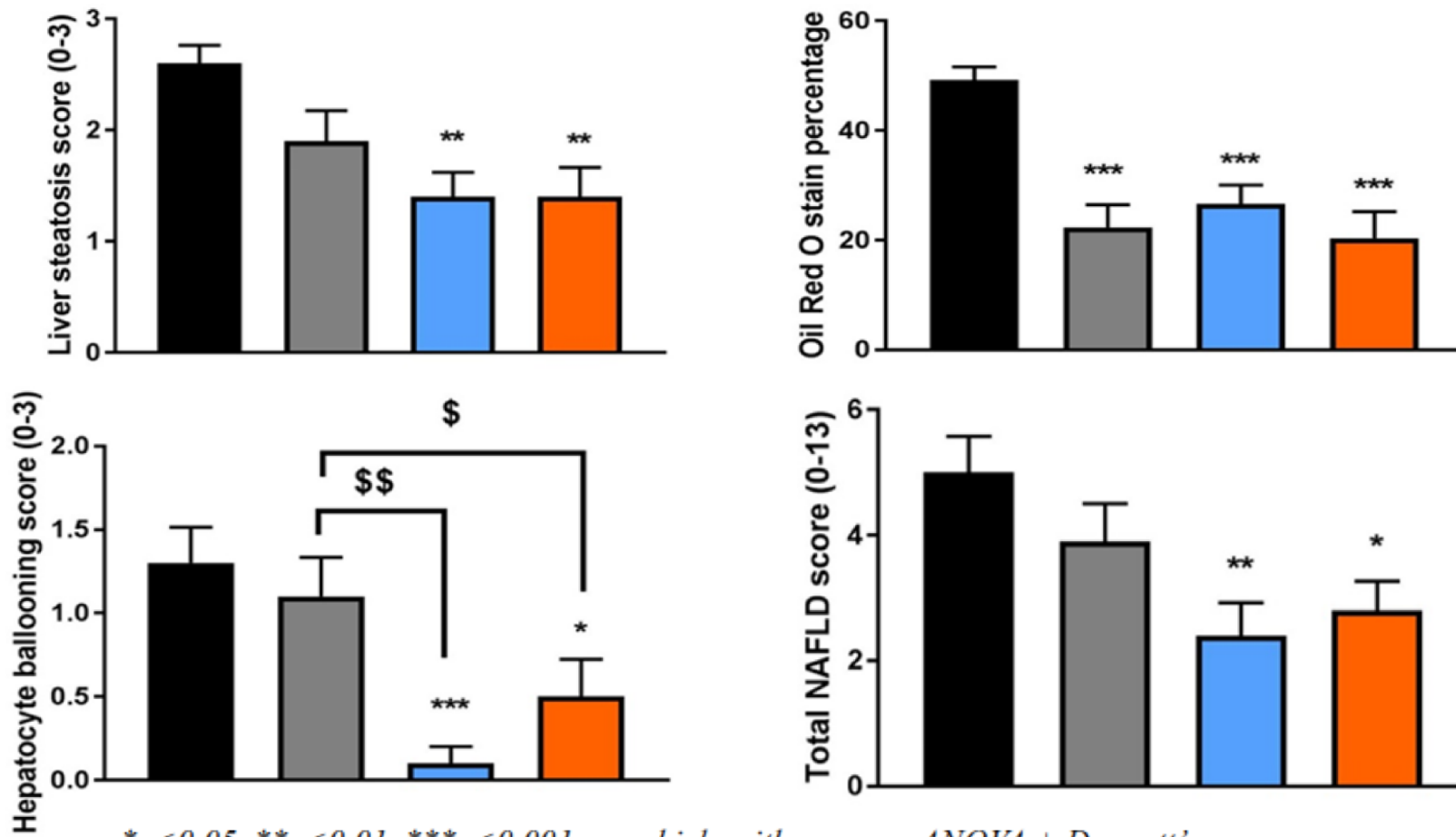


\* $p < 0.05$ , \*\* $p < 0.01$  and \*\*\* $p < 0.001$  vs. vehicle with two-way ANOVA + Bonferroni's;

**ENANTA** Pharmaceuticals  $p < 0.05$  with one-way ANOVA + Newman-Keuls

# EDP-305 decreases liver steatosis, ballooning and NAS (wk16)

- Vehicle
- OCA 30 mg/kg
- EDP-305 10 mg/kg
- EDP-305 30 mg/kg



\* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$  vs. vehicle with one way ANOVA + Dunnett's;

\$ $p < 0.05$  and \$\$ $p < 0.001$  with one way ANOVA + Newman-Keuls

## Conclusions & EDP-305 development

- EDP-305 is a potent FXR agonist with no/minimal activity against other nuclear receptors and TGR5
- Treatment with EDP-305 had a significant therapeutic effect on NASH progression in preclinical animal models
- EDP-305 significantly decreased liver steatosis, hepatocyte ballooning, and total NAS in NASH mouse models
- These results warrant further clinical study of EDP-305 for the treatment of NASH and PBC
- Phase 1 study in healthy subjects and subjects with presumed NAFLD has recently been completed
- Fast Track Designation has been granted by FDA

# Acknowledgement

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