



**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**

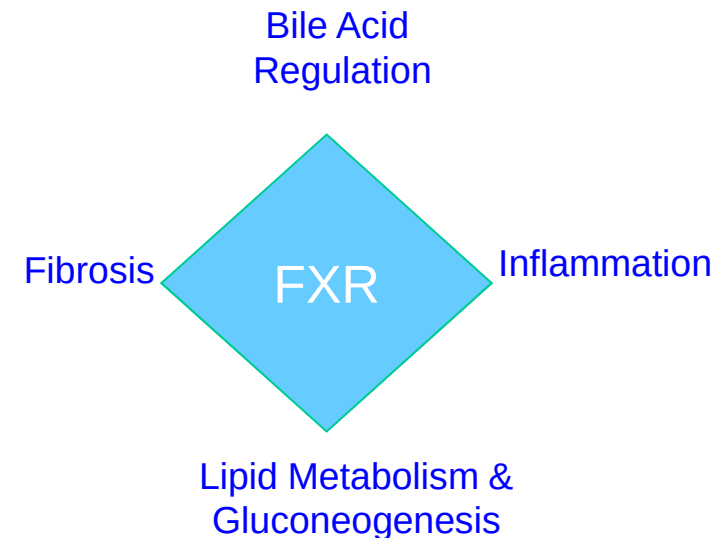
Li-Juan Jiang, Ph. D.

Enanta Pharmaceuticals, Inc. Watertown, MA

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

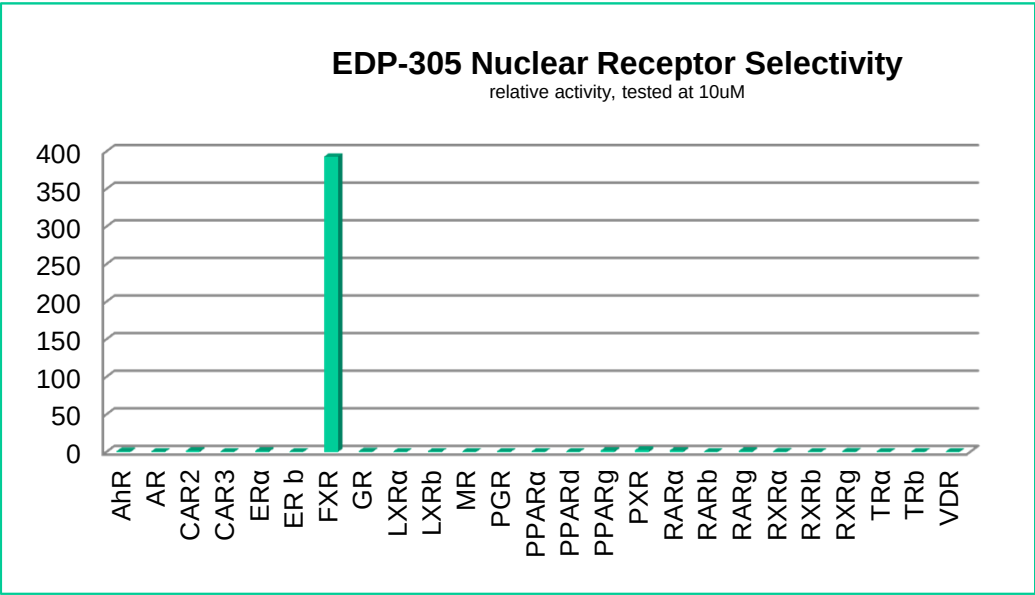
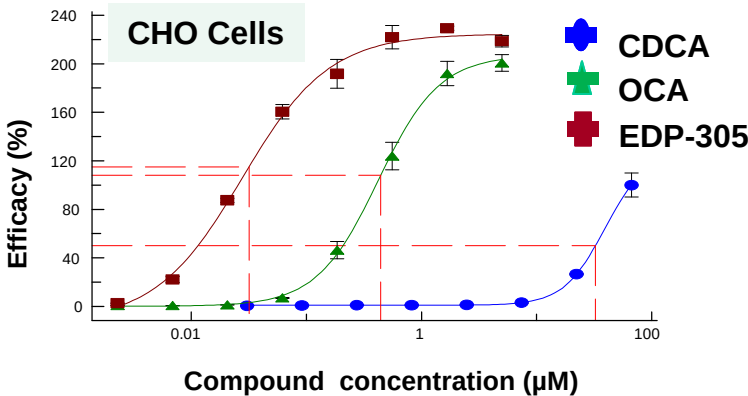


EDP-305 is a potent and selective FXR agonist

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)
EDP-305	8 (152)	> 15,000 (NS)

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



EDP-305 regulates key gene expression

In vitro

- **Bile acid metabolism**
 - SHP; FGF19; OST- α ; BSEP; CYP7A1
- **Lipid metabolism**
 - LDLR; PCSK9; SREBP-1C; SCD1; CD36; DGAT2; APOB; APOC3; HL; SRB1
- **Inflammation**
 - NF- κ B; TLR2; TLR9; TNF α ; IL8; IL1 α ; IL1 β ; IL1R1; CCL2; CCR1; CCR4; CEBPB
- **Fibrosis**
 - α -SMA; TIMP1; TIMP2; PDGF α ; PDGF β ; COL1A2; COL3A1; ITGB6
- **Glucose metabolism**
 - FGF21; IRS2; GLUT2; GLUT4; FOXO1



Up regulation

Down regulation

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

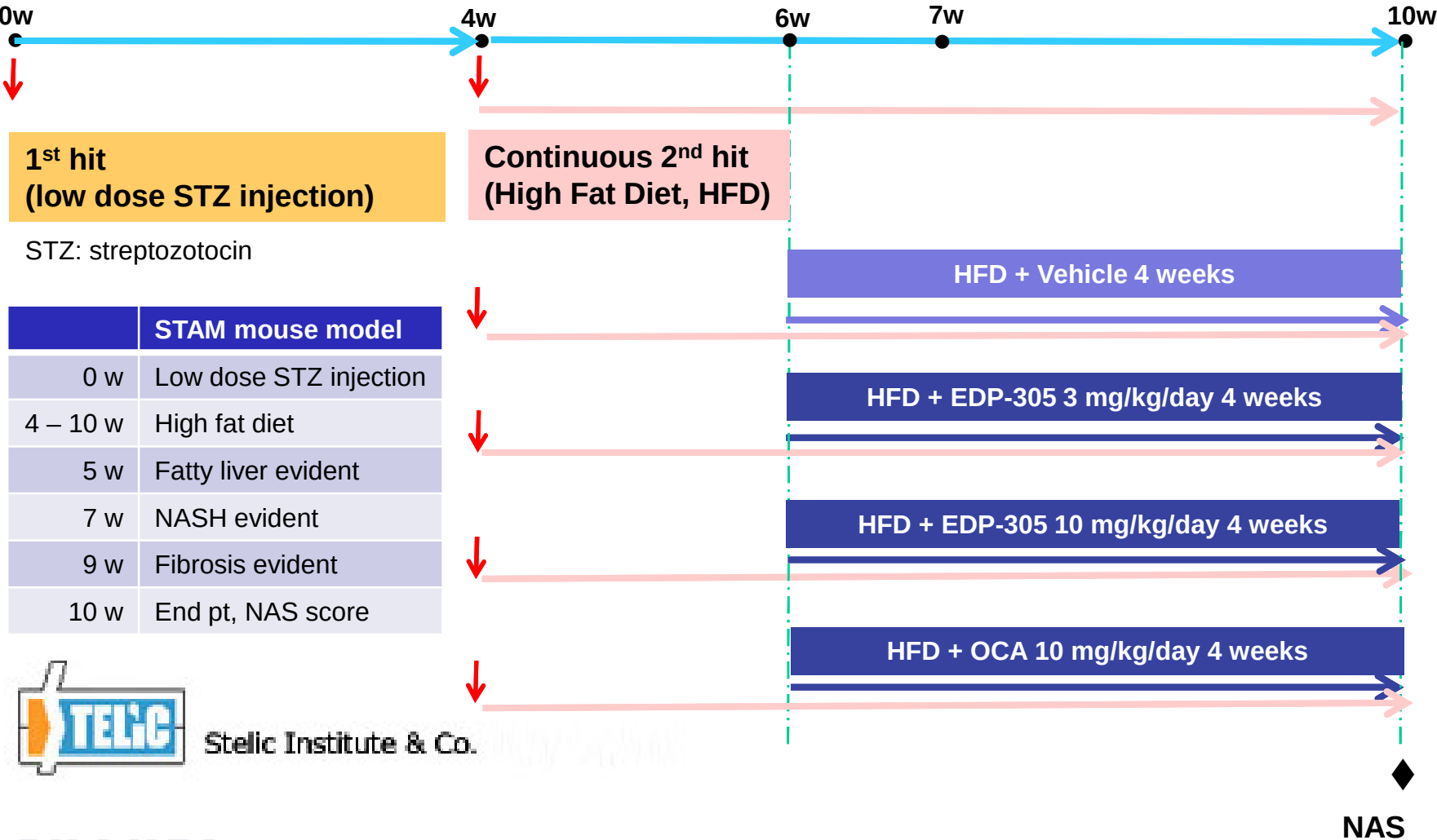
- Mouse model
 - FXR mechanism of action: SHP, CYP7A1 and FGF15 (Enanta Pharmaceuticals, Inc.)
- Liver fibrosis/cirrhosis model
 - Thioacetamide-induced rat liver fibrosis/cirrhosis model (Icahn School of Medicine at Mt. Sinai)
- Biliary fibrosis models
 - Mdr2^{-/-} mouse biliary fibrosis model (Harvard/BIDMC)
 - 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)
 - STAMTM 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



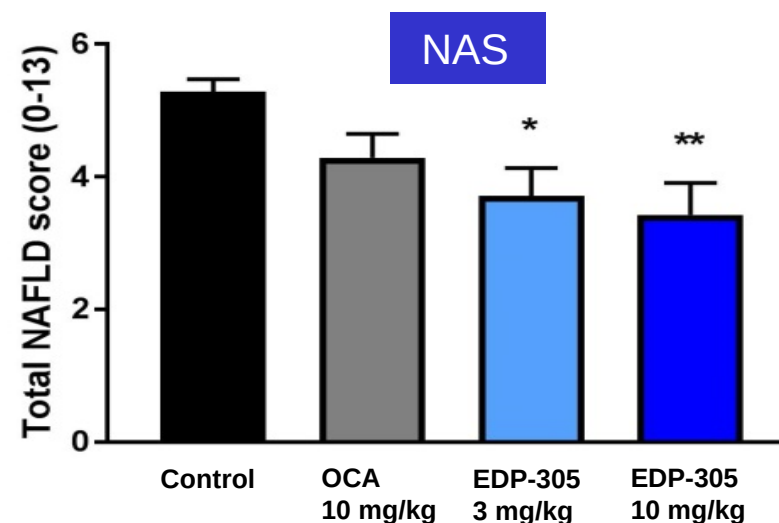
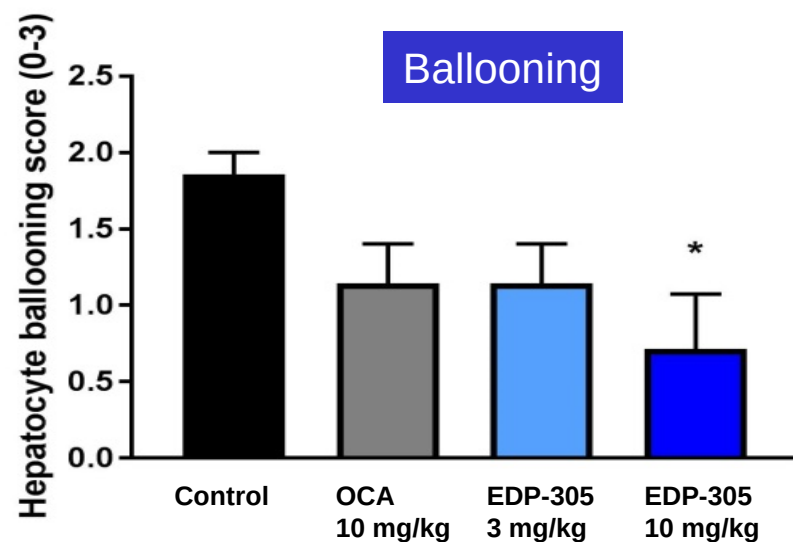
Stellic Institute & Co.

EDP-305 vs OCA in STAM™ mouse model

Non-alcoholic fatty liver disease activity score (NAS)

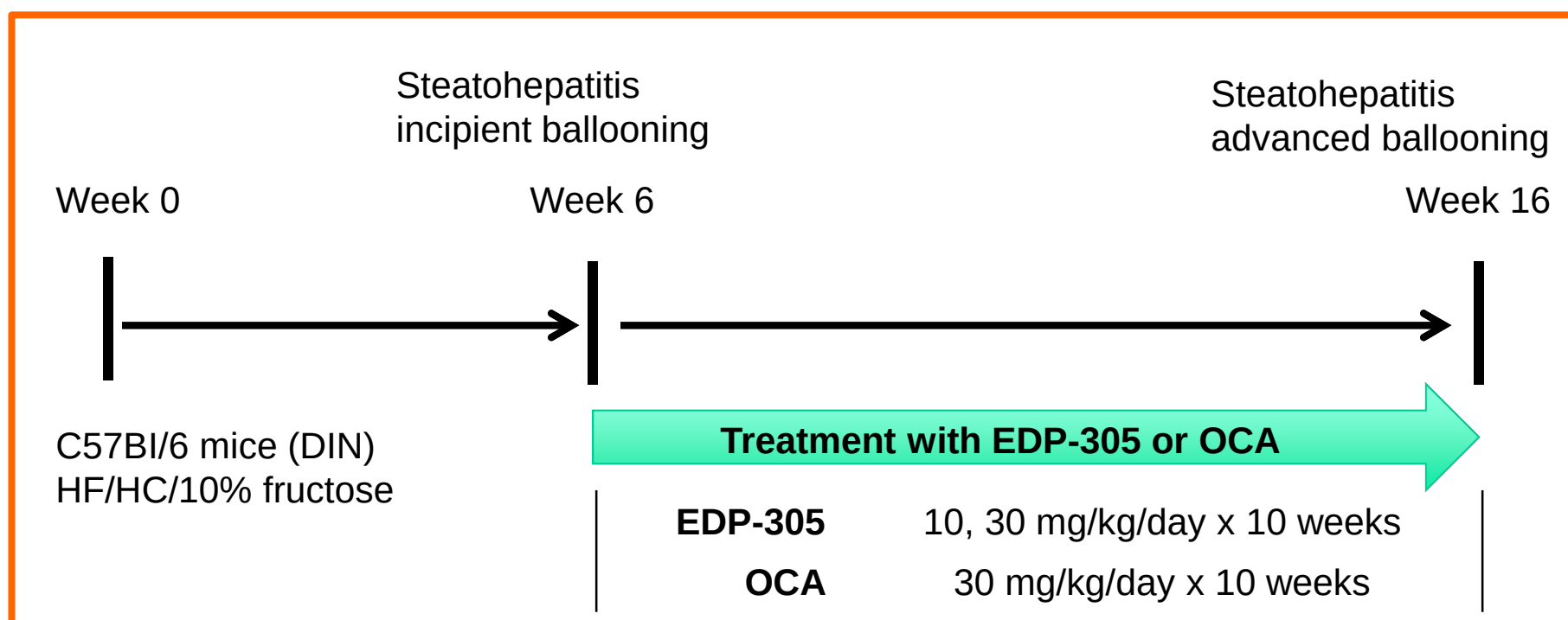
Drug	mg/kg/d	n	Hepatocyte Ballooning Score	NAS
Control	--	7	1.9	5.3
OCA	10	7	1.1	4.3
EDP-305	3	7	1.1	3.7*
EDP-305	10	7	0.7*	3.4**

* p<0.05; ** p<0.01



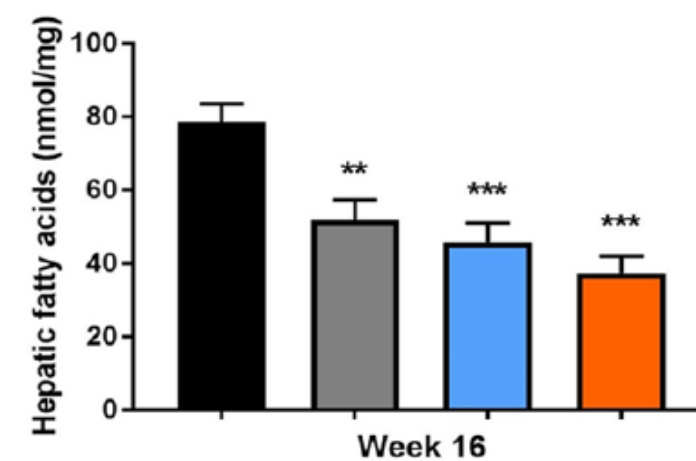
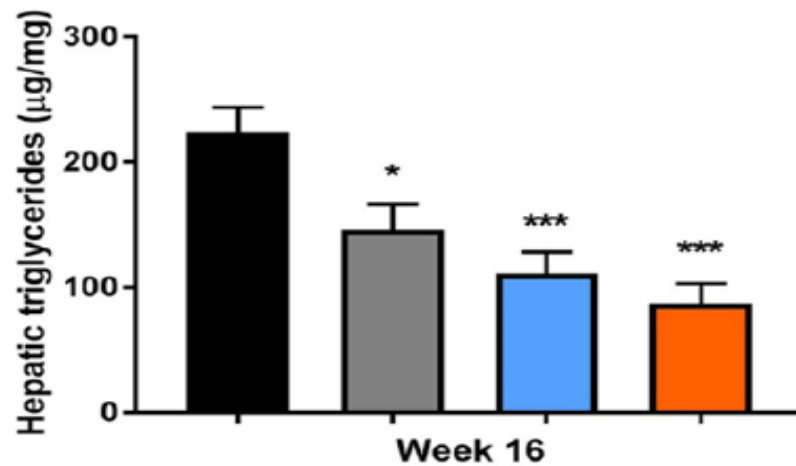
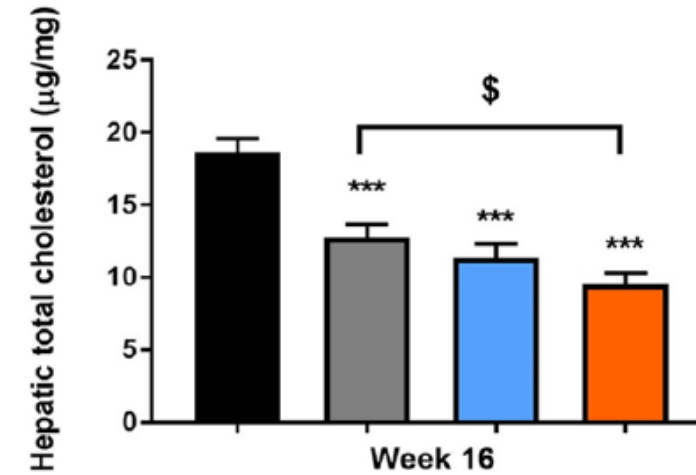
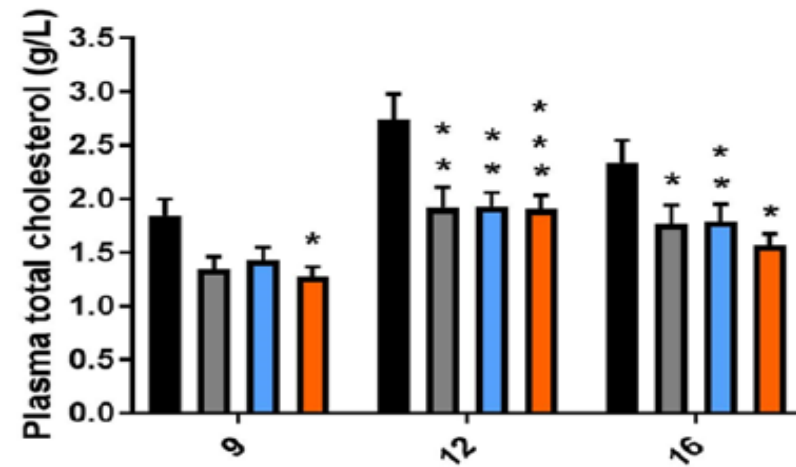
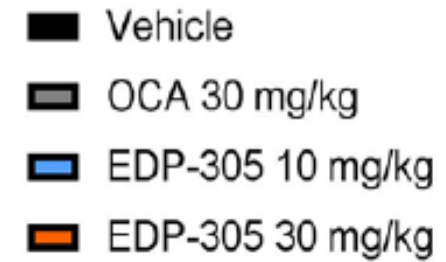
Diet-induced NASH (DIN) Mouse Model

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



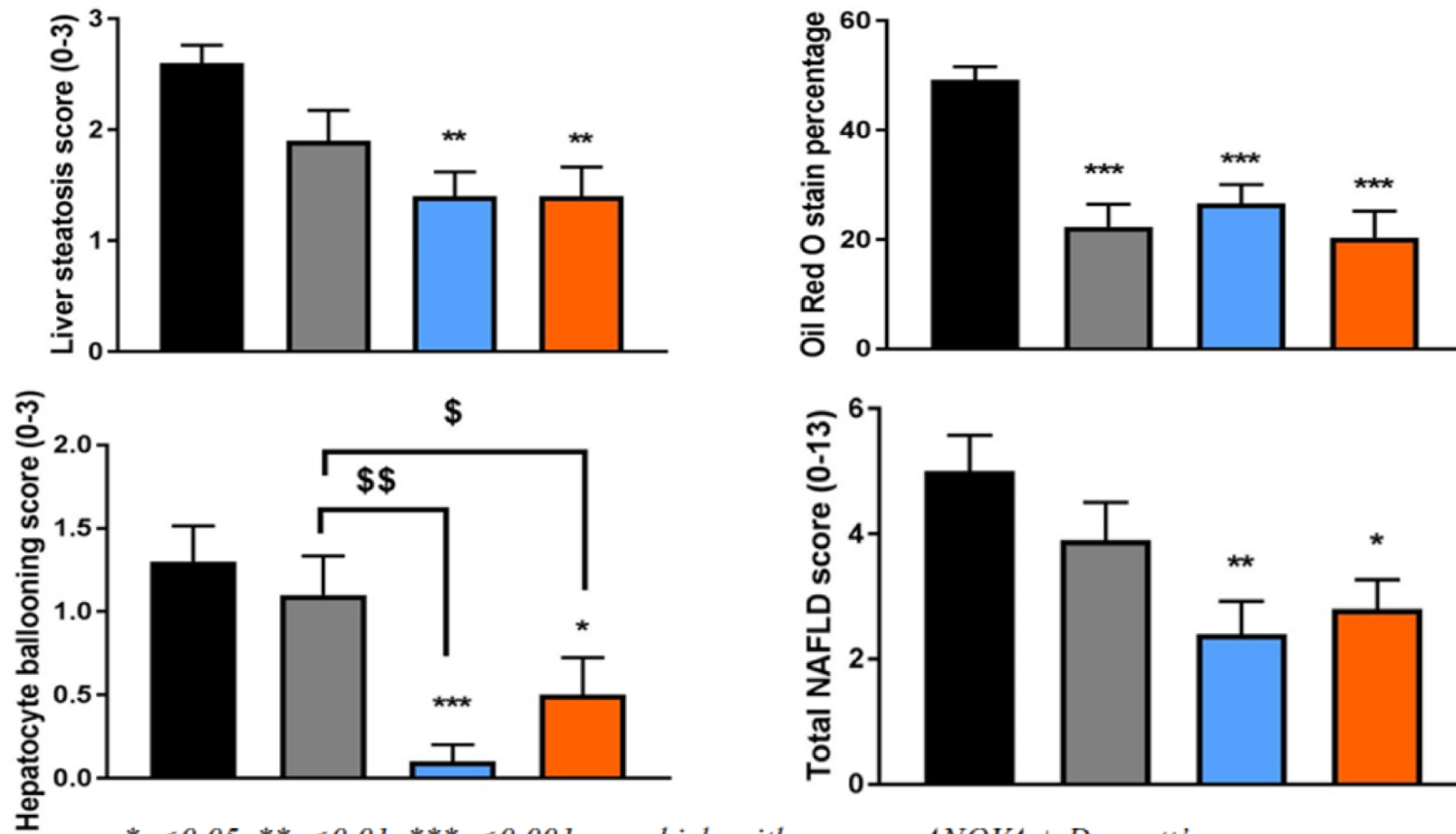
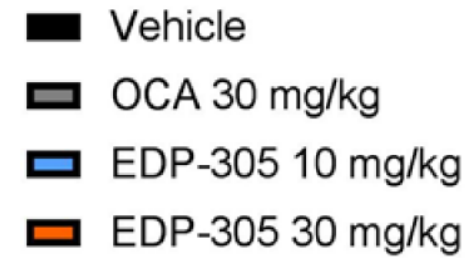
EDP-305 significantly decreased liver steatosis, hepatocyte ballooning, and total NAS in diet-induced NASH (DIN) mice model.

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;

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



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

Enanta

Yat Sun Or
Yang Li
Mary Chau
Manuel Roqueta-Rivera
Kelsey Garlick
Jianyu Shang
Guoqiang Wang
Ruichao Shen
Yong He
Jiang Long
Bin Wang
Jun Ma
Brett Granger

Stelic, Japan

Taishi Hashiguchi
Yuichiro Shibazaki

Physiogenex, France

François Briand
Thierry Sulpice

**THANKS FOR
YOUR ATTENTION**