

The Liver Meeting® 2017 in Washington D.C.

Significant anti-fibrotic efficacy of EDP-305, a highly potent and selective farnesoid X receptor (FXR) agonist, in a rat model of thioacetamide-induced liver fibrosis and cirrhosis

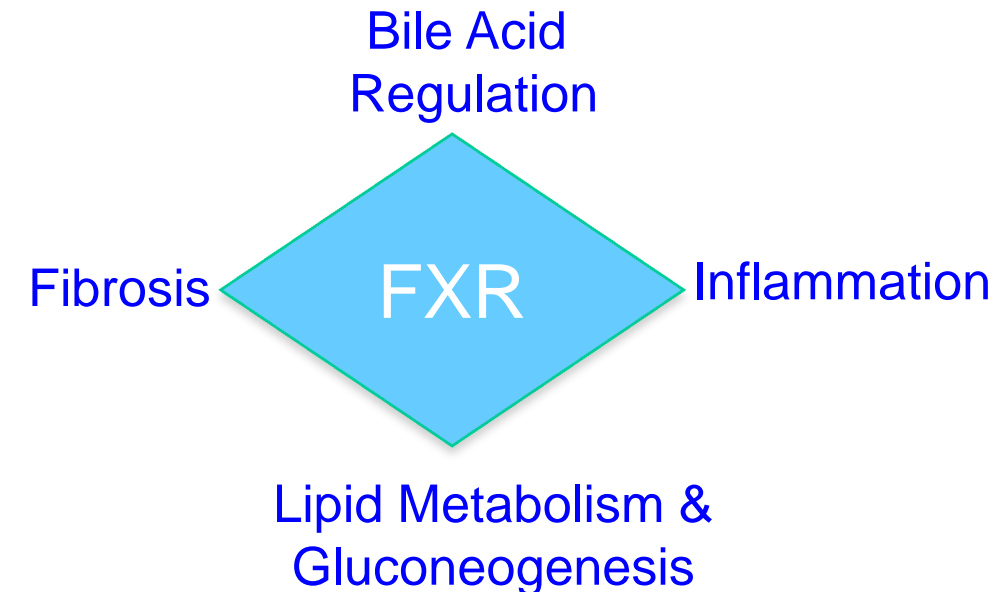
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FXR has emerged as an attractive target for the treatment of NASH & PBC

NASH = nonalcoholic steatohepatitis; PBC = primary biliary cholangitis

- 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

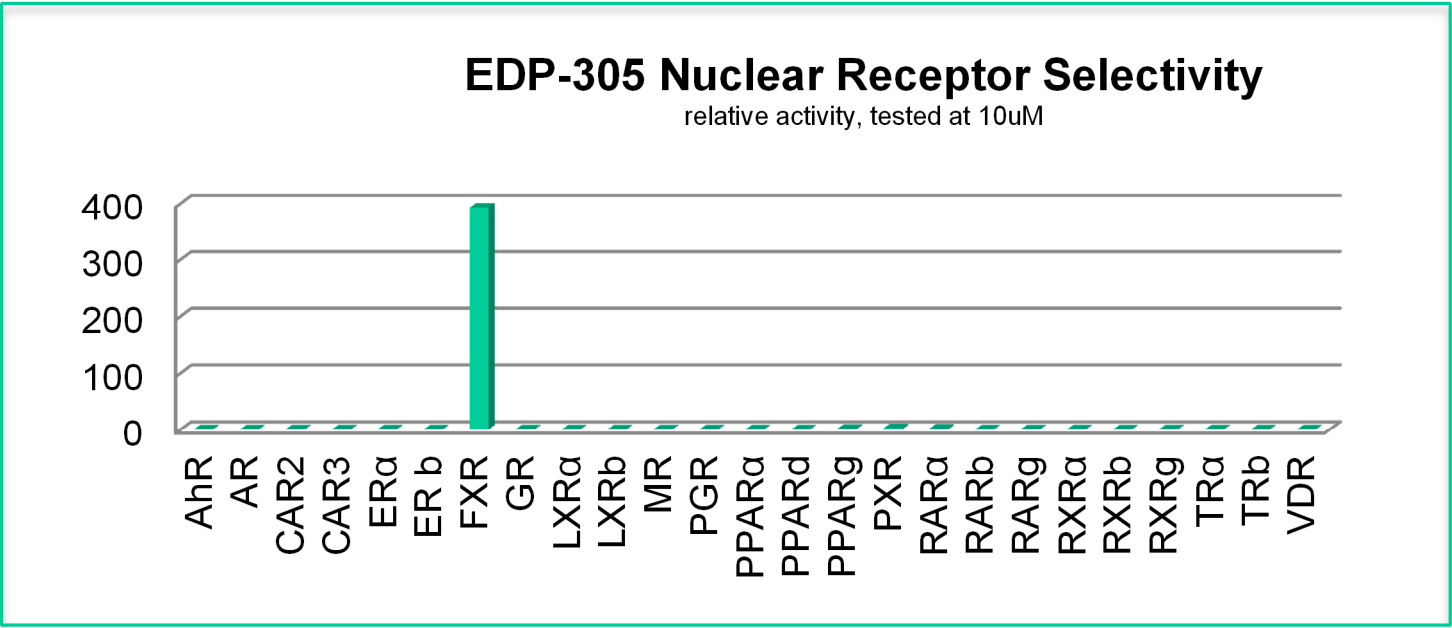
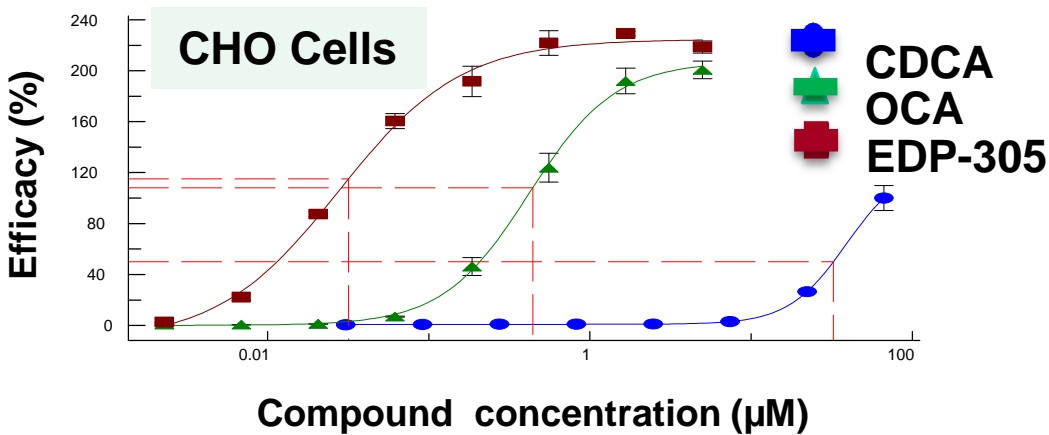


EDP-305 is a potent and selective FXR agonist

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%

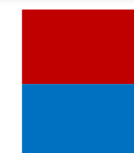


EDP-305 regulates key gene expression

In vitro

- **Bile acid metabolism**

- SHP; FGF19; OST- α ; BSEP; CYP7A1



Up regulation

Down regulation

- **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

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

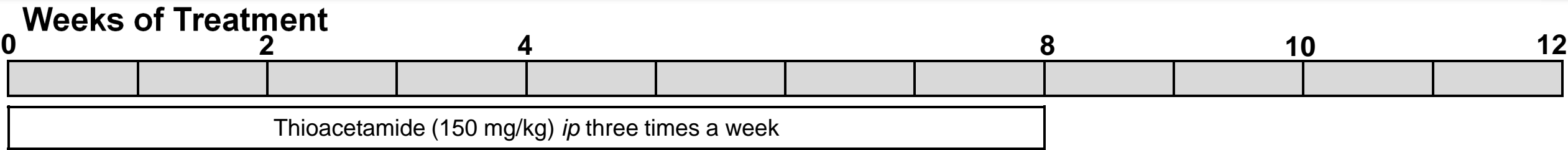
- Mouse model
 - FXR mechanism of action: SHP, CYP7A1 and FGF15 (Enanta Pharmaceuticals, Inc.)
- NASH models
 - STAM™ mouse NASH model (Stelic, Japan)
 - MCD-fed mouse steatohepatitis model with progressive fibrosis (Harvard/BIDMC)
 - Choline-deficient, L-amino acid-defined, high-fat-diet, mouse NASH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

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)

Rat model of thioacetamide(TAA)-induced liver fibrosis and cirrhosis

Study design



Therapeutic Intervention

Oral dosing, QD
<ul style="list-style-type: none">EDP-305, 10 mg/kg/day, n=10EDP-305, 30 mg/kg/day, n=10
<ul style="list-style-type: none">Vehicle, n=10

Cirrhosis Reversal

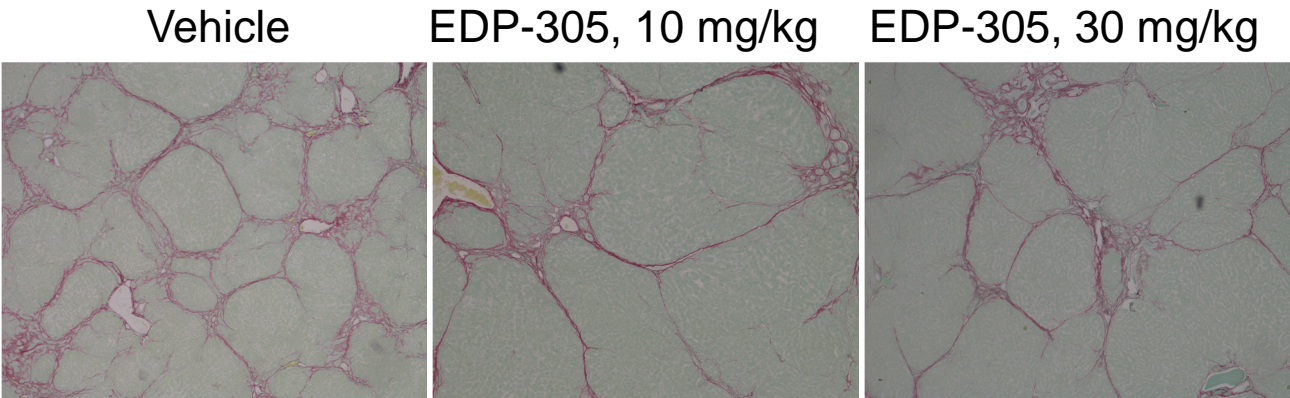
Oral dosing, QD
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<ul style="list-style-type: none">Vehicle, n=10

Weeks	Event
0 - 8	TAA <i>ip</i> injection three times per week
4	Rats develop fibrosis by week 4
4 - 8	Compound concurrently with TAA (Therapeutic Intervention)
8	Rats develop cirrhosis by week 8. Endpoint 1: fibrosis reduction
8 - 12	Compound w/o TAA (Cirrhosis Reversal)
12	Endpoint 2: cirrhosis reversal

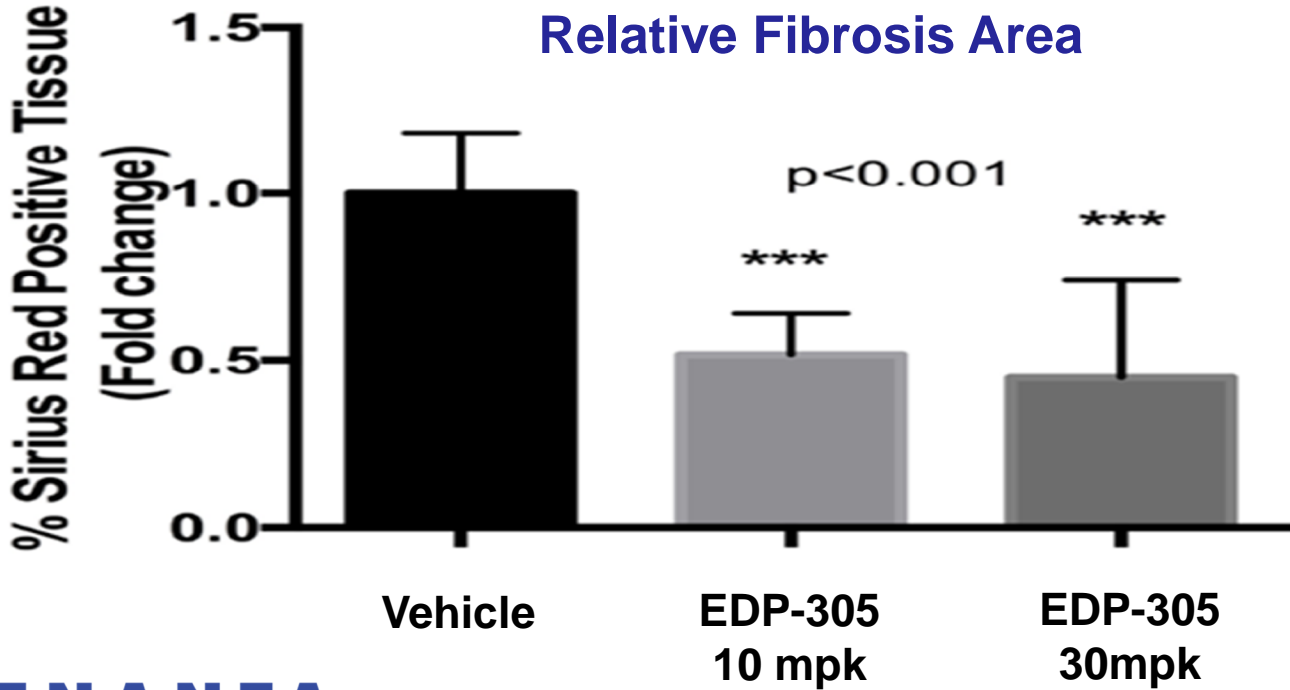
- Endpoints:
- Histopathologic analyses (including Sirius Red staining & pathology scores)
- Serum clinical chemistry
- Weight: body, liver & spleen
- Key fibrogenic gene expression

EDP-305 significantly reduced fibrosis progression in rats

Therapeutic Intervention Results



	Sirius red positive tissue (%)	Reduction in fibrosis (%)
Vehicle	100 %	--
EDP-305 10 mpk	50 %	50 % ↓
EDP-305 30 mpk	45 %	55 % ↓



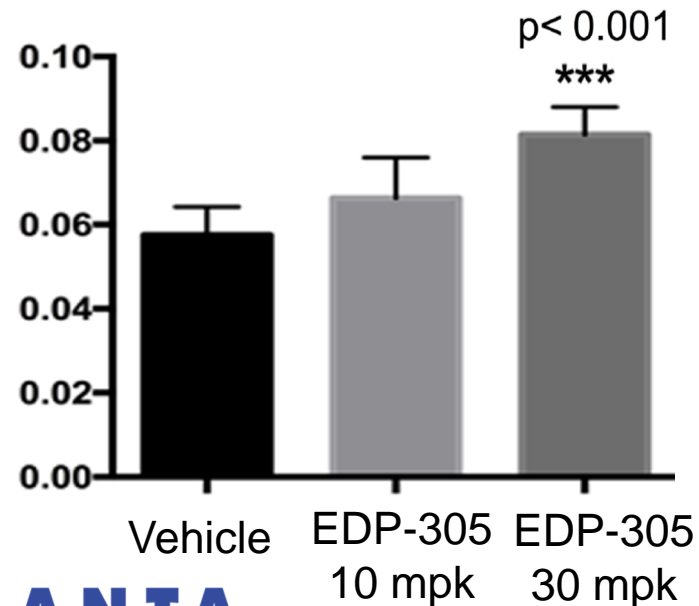
- Pathology scores (including Scheuer score, Ishak score, Ductular reaction/Metaplasia scoring) also decreased in parallel with collagen morphometry

EDP-305 significantly improved liver/spleen weights & serum clinical chemistry

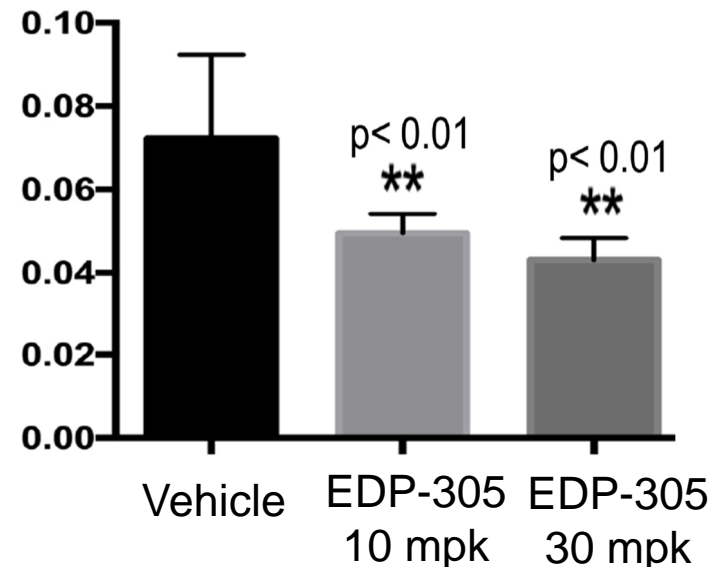
Therapeutic Intervention Results

- Progression of fibrosis/cirrhosis causes liver to body weight ratios to decrease, spleen to liver weight ratios to increase (Splenomegaly), and serum AST levels to increase
- EDP-305 significantly reduced the progression of fibrosis, which led to increased liver to body weight ratios and decreased spleen to liver weight ratios. EDP-305 also improved serum clinical chemistry (e.g., AST) for liver function testing

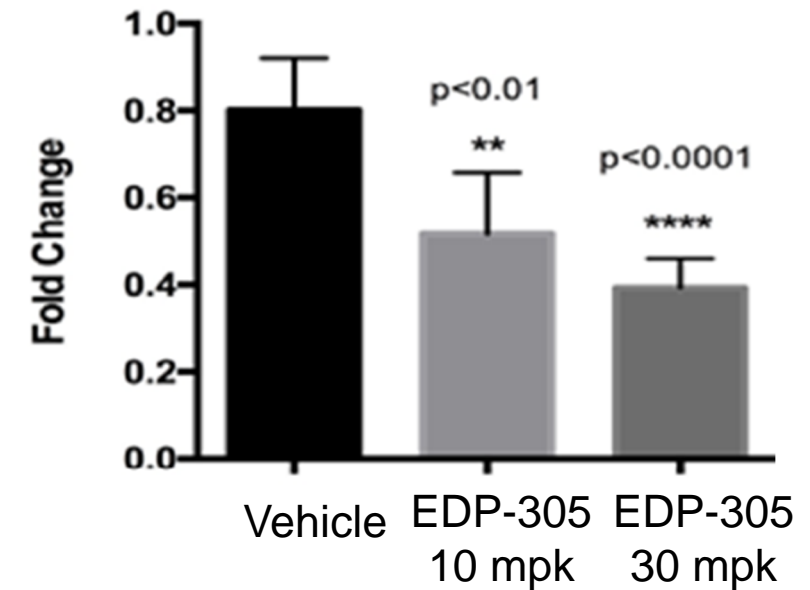
Liver to body weight ratio



Spleen to liver weight ratio

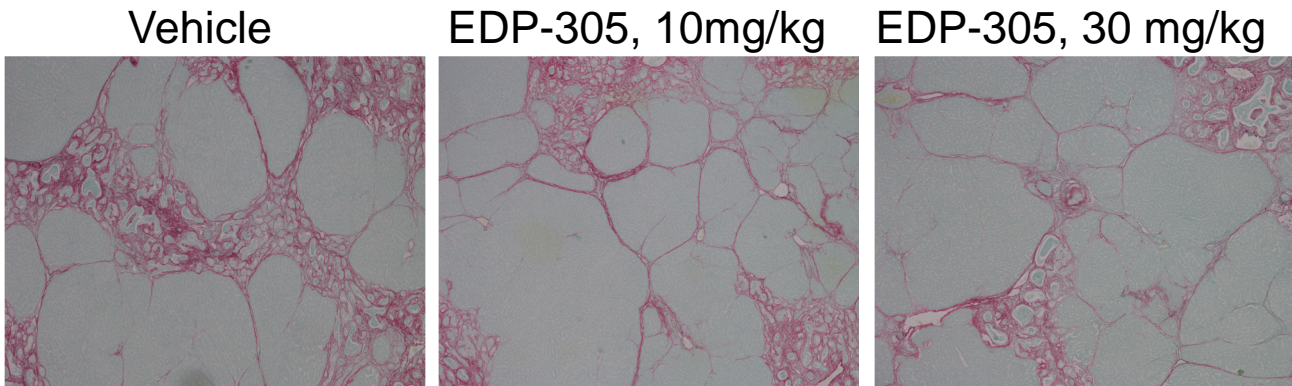


Serum AST

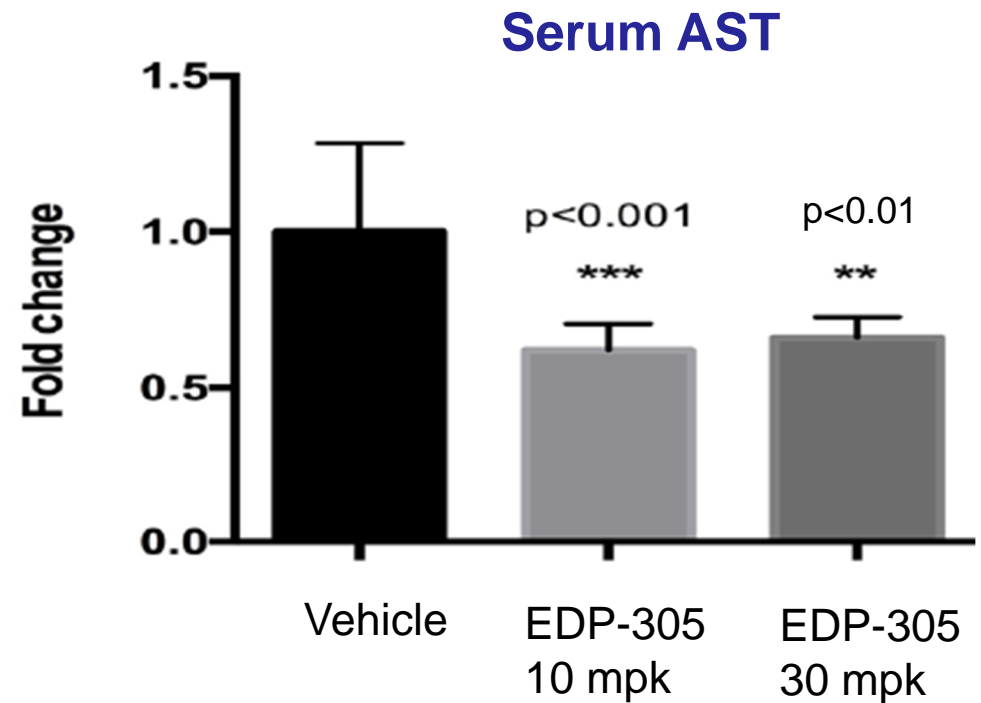
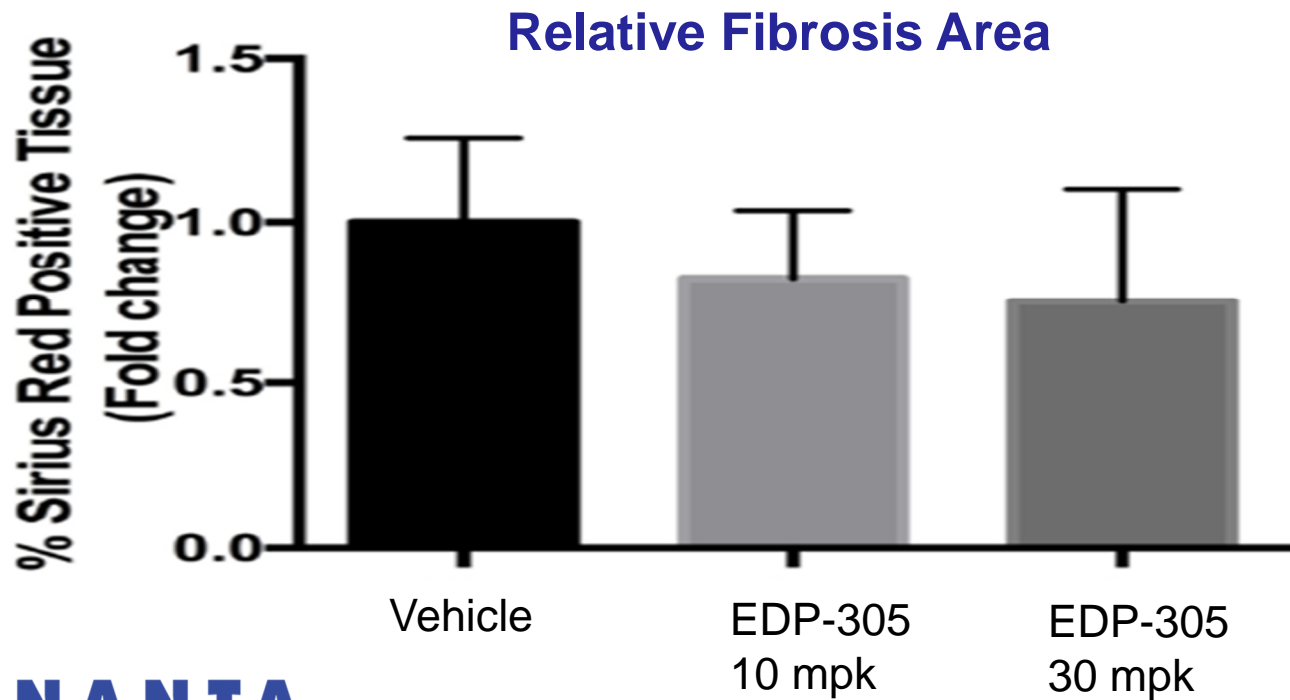


EDP-305 decreases collagen deposition in rats with established cirrhosis

Cirrhosis Reversal Results

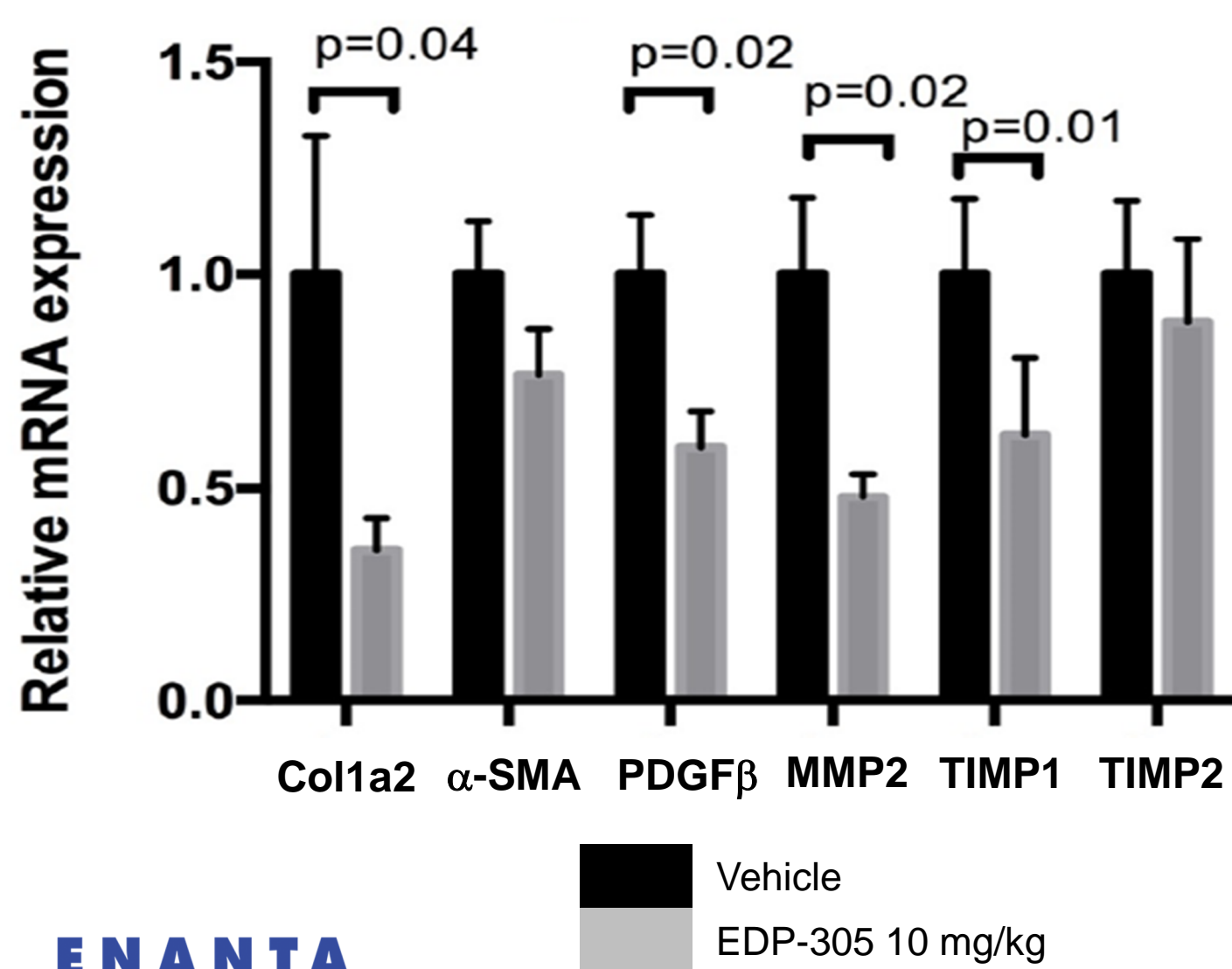


	Sirius red positive tissue (%)	Reduction in fibrosis (%)
Vehicle	100 %	--
EDP-305 10 mpk	89 %	11 % ↓
EDP-305 30 mpk	75 %	25 % ↓



EDP-305 down-regulated key fibrogenic genes

Cirrhosis Reversal Results



	% Reduction compared to vehicle
Collagen type1 alpha 2 (Col1a2)	65% ↓
Alpha smooth muscle actin (α-SMA)	23% ↓
Platelet derived growth factor β (PDGFβ)	40% ↓
Matrix metalloproteinase 2 (MMP2)	52% ↓
Tissue inhibitor of metalloproteinase-1 (TIMP1)	37% ↓
Tissue inhibitor of metalloproteinase-2 (TIMP2)	11% ↓

Conclusions & EDP-305 development

- EDP-305 is a potent FXR receptor agonist with no/minimal activity against other nuclear receptors and TGR5
- EDP-305 exhibits excellent anti-fibrotic efficacy in rats with ongoing TAA-induced fibrosis
- It also decreases collagen deposition in rats with established cirrhosis
- 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

EDP-305 posters in this meeting

- “A novel FXR agonist EDP-305 potently suppresses hepatic stellate cell activation and hepatic fibrosis in chronic mouse models of biliary and metabolic liver disease” (#367)
 - Presented from 8 am – 5:30 pm on Oct 20
- “EDP-305 favorably regulates lipoprotein mechanism *in vitro*” (#1988)
 - Selected as “Presidential Poster of Distinction”
 - To be presented from 8 am – 5:30 pm today (Oct 23)

Acknowledgement

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**THANKS FOR YOUR
ATTENTION**