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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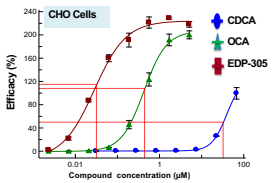
Background

EDP-305, a selective and potent small molecule FXR agonist, is currently in clinical development for the treatment of non-alcoholic steatohepatitis (NASH) and primary biliary cholangitis (PBC). EDP-305 regulates the expression of key genes in the bile acid metabolism, lipid metabolism, inflammation, fibrosis and glucose metabolism. Herein we report the therapeutic efficacy of EDP-305 in two murine models of NASH: Diet Induced NASH (DIN) model and STAM™ model.

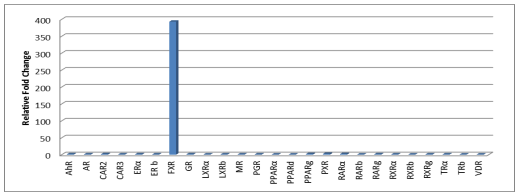
EDP-305 is a potent and selective FXR agonist

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 is Highly Selective for FXR



EDP-305 regulates key gene expression

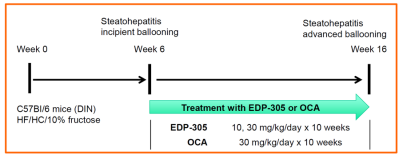
- **Bile acid metabolism**
  - SHP; FGF19; OST-α; BSEP; CYP7A1
- **Lipid metabolism**
  - LDLR; PCSK9;SREBP-1C; SCD1; CD36; DGAT2; APOB; APOC3; HL; SRB1
- **Inflammation**
  - NF-κB; TLR2; TLR9; TNFα; IL8; IL1α; IL1β; IL1R1; CCL2; CCR1; CCR4; CEBPB
- **Fibrosis**
  - α-SMA; TIMP1; TIMP2; PDGFα; PDGFβ; COL1A2; COL3A1; ITGB6
- **Glucose metabolism**
  - FGF21; IRS2; GLUT2; GLUT4; FOXO1

Methods

In the DIN model, NASH was induced in C57Bl/6 mice with a high fat, high cholesterol diet plus 10% fructose in drinking water. All treatments were administered between 6 weeks (steatohepatitis with incipient ballooning) and 16 weeks (advanced steatohepatitis with advanced ballooning). Treatments included: EDP-305 (10 or 30 mg/kg), or vehicle control (n=10/group). In the STAM™ model, NASH was induced in C57Bl/6 by a single subcutaneous injection of 200 μg streptozotocin 2 days after birth, followed by feeding with a high fat diet starting at 4 weeks of age. All treatments were administered between 4 weeks and 10 weeks. Treatments included: EDP-305 (3 or 10 mg/kg), or vehicle control (n=8/group). Liver injury, progression of NASH, liver steatosis, and ballooning were evaluated by serum chemistry and histology.

Results

Diet-induced NASH (DIN) Mouse Model



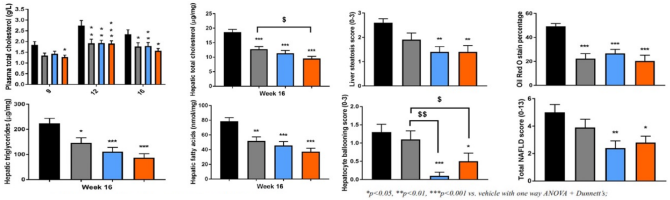


Fig 1. EDP-305 reduces plasma and liver lipid content in the DIN mouse. A. Plasma total cholesterol levels in DIN mice treated with vehicle, EDP-305 10 mg/kg, EDP-305 30 mg/kg, and OCA 30 mg/kg. Hepatic total cholesterol (B), triglycerides (C), and fatty acid (D) levels in DIN mice.

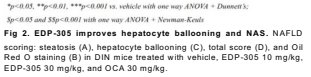
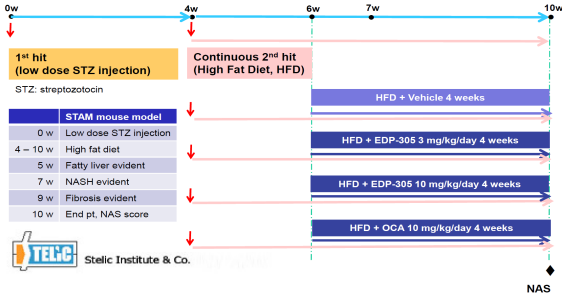


Fig 2. EDP-305 improves hepatocyte ballooning and NAS. NAFLD scoring: steatosis (A), hepatocyte ballooning (C), total score (D), and Oil Red O staining (B) in DIN mice treated with vehicle, EDP-305 10 mg/kg, EDP-305 30 mg/kg, and OCA 30 mg/kg.

*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

- In the DIN model, EDP-305 significantly reduced hepatic cholesterol, triglycerides, and fatty acids by 48.4%, 61.1% and 52.5%, respectively, versus vehicle control.
- Consistent with the observed reductions in liver lipids, liver steatosis was significantly decreased in EDP-305-treated mice (p<0.01).
- EDP-305 significantly reduced total NAS in both treatment groups, consistent with decreased expression of key genes involved in inflammation (MCP-1 and TGF-β) and fibrosis (TIMP-1 and α-SMA).
- EDP-305 significantly decreased liver steatosis, hepatocyte ballooning, and total NAS in diet-induced NAS (DIN) mice model.

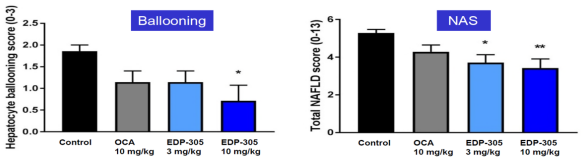
STAM™ mouse model



STAM mouse model	
0 w	Low dose STZ injection
4 – 10 w	High fat diet
5 w	Fatty liver evident
7 w	NASH evident
9 w	Fibrosis evident
10 w	End pt, NAS score

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



In the STAM™ model, EDP-305 significantly reduced hepatocyte ballooning scores as well as total NAS.

Conclusions

Treatment with EDP-305 had a significant therapeutic effect on NASH progression in NASH mouse models, resulting in decreased liver steatosis, hepatocyte ballooning, and total NAS. These results warrant further investigation of EDP-305 as a potential therapy for NASH.

Acknowledgements

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References

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2. Friedman, et al., AASLD presentation (2005)