Decreases in serum 7-alpha-hydroxy-4-cholesten-3-one (C4) correlate well with anti-fibrotic efficacy of EDP-305 in nonalcoholic steatohepatitis (NASH) and biliary fibrosis animal models

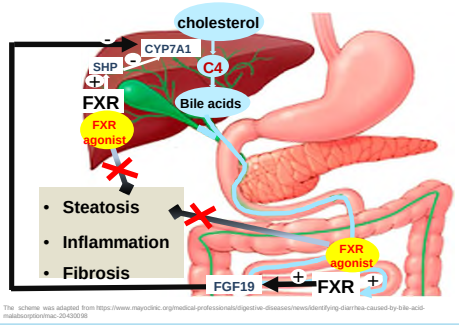
Shucha Zhang[1], Yang Li[1], Madison Adams[1], Yury V. Popov[2], Yat Sun Or[1] and Li-Juan Jiang[1]
[1]Enanta Pharmaceuticals, Inc., Watertown, MA, USA
[2]Divison of Gastroenterology and Hepatology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

ENANTA Pharmaceuticals

P# 2137

Introduction

Serum 7-alpha-hydroxy-4-cholesten-3-one (C4) is a non-invasive biomarker for target engagement of Farnesoid X Receptor (FXR) agonist. Herein, we studied, in multiple nonclinical models, the correlation of C4 reduction with anti-fibrotic effects of EDP-305, a novel and potent FXR agonist currently in Phase 2 clinical trials for NASH[1] and Primary Biliary Cholangitis (PBC)[2].



Methods

***Animal models and EDP-305 dosing*[3,4]**

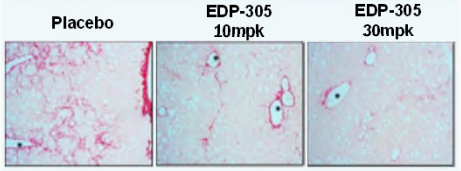
- **Methionine/choline-deficient (MCD) diet-induced C57Bl/6 mouse model of NASH**
  Oral 10 and 30 mg/kg/day. Duration: 4 weeks.
- **BALB/c.Mdr2(abcb4)-/-mouse model of biliary fibrosis**
  Oral 10 and 30 mg/kg/day. Duration: 6 weeks.
- **Thioacetamide(TAA)-induced Wistar rat model of liver cirrhosis**
  Oral 10 and 30 mg/kg/day. Duration: 8 weeks.
- **Cynomolgus monkeys (normal)**
  Oral 25, 50, 100, and 200 mg/kg/day. Duration: 14 days.

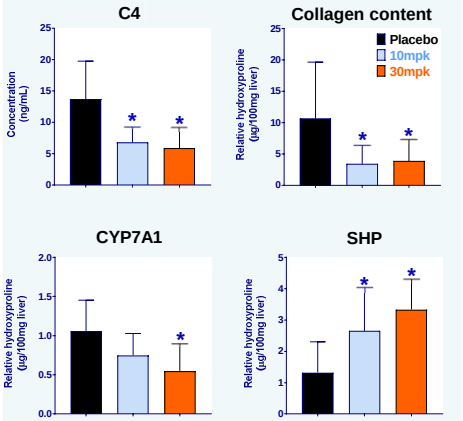
Serum C4 and liver biochemical measurements

- Steady-state serum C4 levels were measured by HPLC/MS/MS.
- Hepatic collagen content was determined biochemically via hydroxyproline content.
- Liver cholesterol 7-alpha-hydroxylase (CYP7A1) and small heterodimer partner (SHP) were determined by RT-PCR.

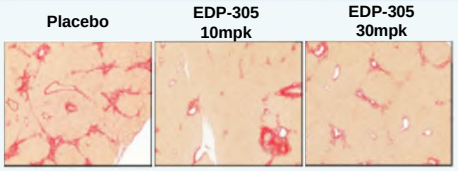
Results

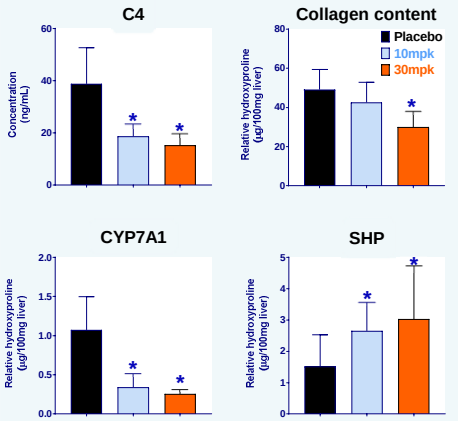
MCD-Diet Mouse Model of NASH



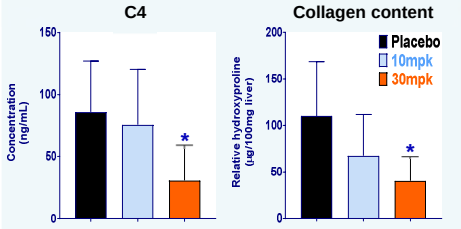


Mdr2-/- Mouse Model of Biliary Fibrosis

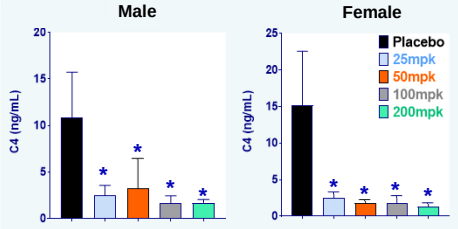




TAA Rat Model of Liver Fibrosis



Monkeys (Normal)



* t-test *p* value < 0.05 compared to placebo

Summary

Table A. C4 and collagen reduction in rodent models of liver fibrosis

Species	Model	Dose (mg/kg)	N	C4 ↓ (%)	Rel Hyp ↓ (%)
MCD-Diet C57Bl/6 Mice	NASH	0	12	0	0
		10	7	50	73
		30	10	57	64
BALB/c.Mdr2-/- Mice	Biliary fibrosis	0	11	0	0
		10	9	51	12
		30	11	62	39
TAA Wistar Rats	Liver fibrosis	0	12	0	0
		10	11	12	39
		30	12	64	63

Table B. C4 reduction in normal male and female monkeys

Species	Model	Dose (mg/kg)	N	C4 ↓ (%)	
				Male	Female
Cynomolgus Monkey	Normal	0	5/5 (M/F)	0	0
		25	5/5 (M/F)	77	83
		50	5/5 (M/F)	71	88
		100	4/5 (M/F)	85	89
		200	4/5 (M/F)	85	91

Conclusions

- ❑ EDP-305 exhibited a strong FXR target engagement by measuring C4 reduction in several preclinical species, including mice, rats and monkeys.
- ❑ Serum C4 reduction correlated very well with anti-fibrotic efficacy of EDP-305 in preclinical NASH and biliary fibrosis models.
- ❑ Current results warrant clinical trials of EDP-305 in the treatment of NASH and PBC.

References

1. ClinicalTrials.gov Identifier: NCT03421431
2. ClinicalTrials.gov Identifier: NCT03394924
3. Popov *et al*, AASLD 2017 poster presentation #367
4. Jiang *et al*. AASLD 2017 oral presentation #162