Pharmacokinetics (PK), Pharmacodynamics (PD), and Safety/Tolerability Effects of EDP-305, a Novel Once-Daily Oral Farnesoid X Receptor (FXR) Agonist in Healthy Subjects and in Subjects with Presumptive Nonalcoholic Fatty Liver Disease (NAFLD)

Alaa Ahmad[1], Kristin Sanderson[1], Daniel Dickerson[2], Nathalie Adda[1].
[1]Enanta Pharmaceuticals Inc., Watertown, MA, United States , [2]PRA Lenexa, KS, United States.

ENANTA Pharmaceuticals

FRI-489

Introduction and Background: EDP-305

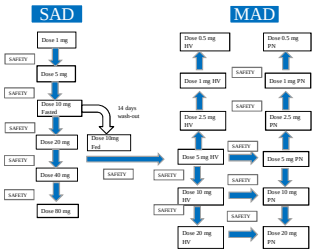
- NASH is considered the fastest-growing cause of cirrhosis, hepatocellular carcinoma and indication for liver transplantation.
- Farnesoid X receptors (FXRs) are nuclear hormone receptors expressed in high amounts in body tissues that participate in bilirubin metabolism including the liver, intestines, and kidneys.
- Farnesoid X receptors regulate the expression of the gene encoding for cholesterol 7-α-hydroxylase, and FXRs play a critical role in carbohydrate and lipid metabolism.
- EDP-305 is a potent, non-bile acid FXR receptor agonist:
  - Highly selective for FXR versus other nuclear receptors and TGR5 receptor
  - Potent effects on FXR-dependent gene expression e.g. *Shp, Cyp7a1, Bsep, Fgf15/Fgf19* in human hepatocytes and *in vivo* mouse model
  - Positively affects lipid metabolism *in vitro*, potentially by increasing LDL clearance *via* up-regulation of LDLr
  - Improvement in hepatocyte ballooning and overall NAFLD Activity Score (NAS) in the STAM™ and dietary-induced NASH (DIN) mouse models
  - Reduced liver fibrosis in multiple rodent models of fibrosis (*e.g.* Mdr2$^{-/-}$ mice, methionine- and choline-deficient diet, thioacetamide, and bile duct ligation)

Methods

Study EDP 305-001 Key Objectives

- To evaluate the safety and tolerability of a single dose of EDP-305 administered to healthy volunteers (HV) and multiple doses of EDP-305 administered to HV and subjects with presumptive NAFLD (PN)
- To evaluate the pharmacokinetics (PK) of single and multiple doses of EDP-305 in plasma and urine
- To evaluate exploratory pharmacodynamics (PD) markers (e.g. FGF19, C4)

Study Design



- Double-blind, placebo-controlled, single- and multiple-dose study in HV and PN subjects (i.e. obese with or without prediabetes or type 2 diabetes mellitus)
- Safety and tolerability assessments evaluated throughout study conduct
  - Adverse events monitoring, clinical laboratory, physical examination and electrocardiographic evaluations performed throughout study
  - Extensive lipid, glucose, and insulin metabolism markers
  - Ultrasound in PN
- PK and PD assessments (MAD only)
  - Intensive sampling over 24 hr for PK on Day 1 (including pre dose on Day 2), and over 96 hr on Day 14 (with additional samples in the morning on day 15, 16, 17 and 18), and additional pre dose samples on Days 3, 4, 5, 7, 9, 12
  - PK parameters estimated using non-compartmental analysis
  - PD measurements included plasma fibroblast growth factor 19 (FGF19) and serum 7-α-hydroxy-4-cholesten-3-one (C4) : samples were collected on Day 1 predose and post dose 2, 4, 6, 8, 12, & 24 hr (i.e., Day 2 predose), and on Days 7 & 14 (predose, 6, 8, 12, & 24 hr)

RESULTS

Subject Enrollment and Demographics

- A total of 146 subjects enrolled: n=50 in SAD; 96 in MAD with 48 HV and 48 PN
- Approximately 60% of subjects with presumptive NAFLD had mild to moderate fatty liver, with 1 severe as shown by ultrasound at entry

Table 1. Demographics in HV and PN subjects during MAD Phase

	Healthy Volunteers							
	EDP-305 0.5 mg (N=6)	EDP-305 1 mg (N=6)	EDP-305 2.5 mg (N=6)	EDP-305 5 mg (N=6)	EDP-305 10 mg (N=6)	EDP-305 20 mg (N=6)	Placebo (N=12)	Overall (N=48)
Male, n (%)	5 (83.3)	5 (83.3)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	11 (91.7)	45 (93.8)
White, n (%)	1 (16.7)	3 (50.0)	4 (66.7)	3 (50.0)	4 (66.7)	4 (66.7)	7 (58.3)	26 (54.2)
Hispanic or Latino, n (%)	0 (0.0)	1 (16.7)	2 (33.3)	0 (0.0)	2 (33.3)	0 (0.0)	1 (8.3)	6 (12.5)
Mean Age (range)	36.7	36.7	38.7	33.0	36.8	32.7	33.4	35.2
	(20, 54)	(24, 55)	(23, 52)	(20, 45)	(20, 49)	(27, 41)	(22, 50)	(20, 55)
Mean BMI (range)	25.82	23.72	26.52	27.02	25.03	27.07	25.10	25.67
	(23.0, 28.4)	(21.3, 26.2)	(22.1, 28.8)	(25.5, 29.5)	(21.8, 28.6)	(24.3, 29.3)	(20.6, 28.2)	(20.6, 29.5)
	Presumptive NAFLD							
	EDP-305 0.5 mg (N=6)	EDP-305 1 mg (N=6)	EDP-305 2.5 mg (N=6)	EDP-305 5 mg (N=6)	EDP-305 10 mg (N=6)	EDP-305 20 mg (N=6)	Placebo (N=12)	Overall (N=48)
Male, n (%)	6 (100.0)	5 (83.3)	5 (83.3)	3 (50.0)	5 (83.3)	5 (83.3)	11 (91.7)	40 (83.3)
White, n (%)	3 (50.0)	1 (16.7)	5 (83.3)	3 (50.0)	3 (50.0)	3 (50.0)	6 (50.0)	24 (50.0)
Hispanic or Latino, n (%)	1 (16.7)	1 (16.7)	2 (33.3)	2 (33.3)	1 (16.7)	0 (0.0)	0 (0.0)	7 (14.6)
Mean Age (range)	32.2	40.0	39.8	38.0	41.8	39.5	42.3	39.5
	(26, 45)	(29, 48)	(31, 47)	(25, 51)	(36, 50)	(25, 49)	(26, 52)	(25, 52)
Mean BMI (range)	32.62	31.48	30.33	31.22	31.38	31.30	32.05	31.55
	(31.4, 33.4)	(28.8, 34.5)	(28.7, 32.9)	(29.9, 34.3)	(29.6, 33.4)	(29.2, 33.3)	(30.5, 34.8)	(28.7, 34.8)

General Safety- MAD Phase

- EDP-305 was generally well tolerated at multiple doses up to 20 mg for 14 days.
- Treatment-emergent adverse events (TEAEs) occurring in ≥ 2 EDP-305 treated subjects were: headache and pruritus in HV, and constipation and pruritus in PN.
- No SAEs or Grade 4 AEs were reported.
- Of the cases of pruritus noted (9% for EDP-305, 3% in placebo), the majority were mild or moderate (except n=1) and occurred at multiple doses of 20 mg (n= 7/12), 10 mg (n=2/12), or placebo (1/24) with 1 drug discontinuation at 20 mg in HV. There were no cases below 10 mg.

Table 2. Treatment-Emergent AEs after multiple doses of EDP-305 in HV and PN (14days)

	Healthy Volunteers							
	EDP-305 0.5 mg (N=6) n (%)	EDP-305 1 mg (N=6) n (%)	EDP-305 2.5 mg (N=6) n (%)	EDP-305 5 mg (N=6) n (%)	EDP-305 10 mg (N=6) n (%)	EDP-305 20 mg (N=6) n (%)	Placebo (N=12) n (%)	Overall (N=48) n (%)
Total Subjects with at Least One TEAE	2 (33.3)	0 (0.0)	0 (0.0)	2 (33.3)	1 (16.7)	5 (83.3)	2 (16.7)	12 (25.0)
Total Number of SAEs	0	0	0	0	0	0	0	0
Total Subjects who Discontinued Treatment Due to an AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	0 (0.0)	2 (4.2)
Total Subjects who Discontinued Study Due to an AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Presumptive NAFLD							
	EDP-305 0.5 mg (N=6) n (%)	EDP-305 1 mg (N=6) n (%)	EDP-305 2.5 mg (N=6) n (%)	EDP-305 5 mg (N=6) n (%)	EDP-305 10 mg (N=6) n (%)	EDP-305 20 mg (N=6) n (%)	Placebo (N=12) n (%)	Overall (N=48) n (%)
Total Subjects with at Least One TEAE	0 (0.0)	3 (50.0)	2 (33.3)	1 (16.7)	1 (16.7)	3 (50.0)	4 (33.3)	14 (29.2)
Total Number of SAEs	0	0	0	0	0	0	0	0
Total Subjects who Discontinued Treatment Due to an AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total Subjects who Discontinued Study Due to an AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

- No clinically significant laboratories were reported except one transient and isolated Grade 2 ALT/AST elevation in n=1 (MAD-HV-20mg) that led to drug discontinuation
- No difference between EDP-305 and PBO was observed for fasting glycemia, HOMA-IR (Homeostasis Model Assessment) Index, and fasting insulinemia in HV and PN
- No significant changes in total cholesterol, HDL, LDL and triglycerides were observed at any dose (except at 20mg in PN for cholesterol and HDL) (Figures 1-4)

Acknowledgments

We extend our thanks to the subjects who participated in this study.

Disclosures

A. Ahmad, K. Sanderson, N.Adda: Enanta Pharmaceuticals Inc.

Lipids

Figure 1: Boxplot of Total Cholesterol Percent Changes from Baseline to Day 14 in HV and PN

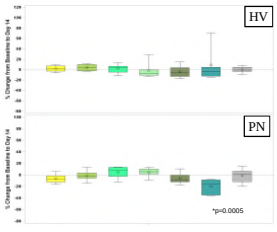
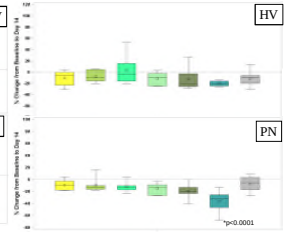


Figure 2:Boxplot of Cholesterol HDL Percent Changes from Baseline to Day 14 in HV and PN



*p value for groups comparison vs. placebo determined using a Student's t-test.

Figure 3: Boxplot of Cholesterol LDL Percent Changes from Baseline to Day 14 in HV and PN

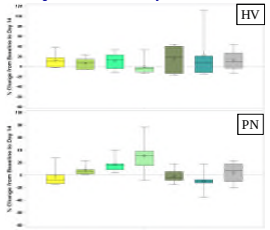
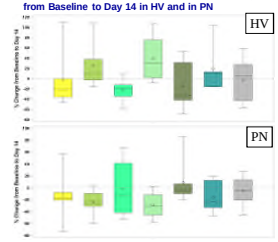


Figure 4: Boxplot of Triglycerides Percent Changes from Baseline to Day 14 in HV and in PN



Pharmacokinetics

Figure 5: EDP-305: Mean Plasma Concentration by Cohorts in HV

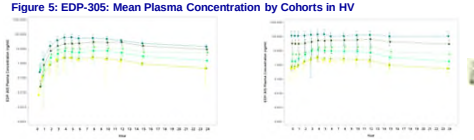


Figure 6: EDP-305: Mean Plasma Concentration by Cohorts in PN

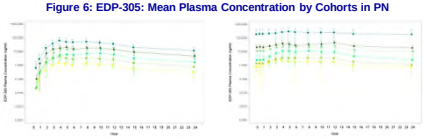


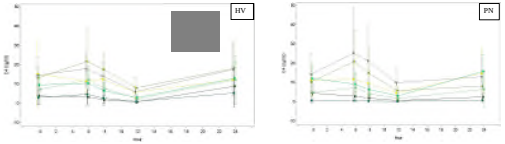
Table 3: PK Parameters following multiple doses, Day 14 in HV and PN

Study Population		Healthy Volunteers						Presumptive NAFLD					
Parameter	Statistic	0.5 mg (N=6)	1 mg (N=6)	2.5 mg (N=6)	5 mg (N=6)	10 mg (N=6)	20 mg (N=6)	0.5 mg (N=6)	1 mg (N=6)	2.5 mg (N=6)	5 mg (N=6)	10 mg (N=6)	20 mg (N=6)
C_{max} (ng/mL)	n	6	6	6	6	6	4	6	6	6	6	6	6
	Mean	2.99	3.69	12.57	22.22	69.52	184.90	2.64	4.50	13.16	32.67	47.88	321.30
	SD	1.43	1.44	2.78	10.31	62.21	150.80	3.08	2.34	11.20	24.72	17.09	282.20
T_{max} (hr)	n	6	6	6	6	6	4	6	6	6	6	6	6
	Mean	5.00	4.70	6.20	8.00	9.30	6.00	5.70	7.70	6.00	5.30	8.20	6.00
	SD	2.45	1.63	2.99	3.58	3.50	4.08	2.94	3.44	2.21	2.34	4.23	3.03
$AUC_{0\text{-}tau}$ (hr*ng/mL)	n	6	6	6	6	6	4	6	6	6	6	6	6
	Mean	32.68	40.62	134.30	280.30	1091.30	3193.00	34.13	57.83	156.77	422.50	691.20	5398.70
	SD	16.39	16.81	48.59	150.40	1009.14	2640.03	40.20	36.13	154.96	322.10	256.69	5173.36
$t_{1/2}$ (hr)	n	6	6	5	6	6	3	6	6	6	5	6	4
	Mean	10.86	11.10	12.80	13.83	15.31	23.17	12.03	12.18	10.15	13.76	17.43	17.50
	SD	2.56	3.63	3.01	3.56	5.26	10.59	3.16	1.97	2.63	2.62	4.62	3.88

- Following single and multiple doses, dose proportional increases in exposure were observed
- Similar exposures were observed in both HV and PN subjects
- EDP-305 was relatively rapidly absorbed, with T_{max} occurring 5-9 h post-dose
- Mean $t_{1/2}$ ranged from 10-18 hours in PN and from 11-23 in HV following multiple doses of EDP-305
- EDP-305 levels in the urine were very low suggesting that urinary excretion is a minor elimination pathway
- Longer $t_{1/2}$ and more drug accumulation (~3-fold) were observed following 20 mg dose compared to lower doses, indicating a potential change in the PK profile at that dose

Pharmacodynamics

Figure 7. Serum C4 at Day14: Plot of Mean (±SD) C4 vs Time in HV and PN



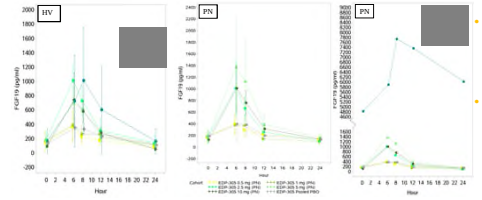
- Reductions of serum C4 over a broad range were observed 12-h post dose at D14 (Table 4, Figure 7)
- All EDP-305 doses led to reductions in serum C4 vs PBO in PN, while doses ≥ 2.5 mg led to reductions in serum C4 vs PBO in HV.

Table 4: Mean Serum C4 (ng/mL) 12H post-dose at Day 14 in HV and PN

		Healthy Volunteers						
Visit/ Timepoint	Statistic	EDP-305 0.5 mg (N=6)	EDP-305 1 mg (N=6)	EDP-305 2.5 mg (N=6)	EDP-305 5 mg (N=6)	EDP-305 10 mg (N=6)	EDP-305 20 mg (N=6)	Placebo (N=12)
Day 1: Baseline	n	6	6	6	6	6	6	12
	Mean	7.88	12.50	24.54	26.05	26.42	25.60	26.09
	Min, Max	1.9, 15.7	2.7, 24.1	3.6, 39.6	1.6, 68.0	5.1, 49.7	4.5, 45.2	4.0, 52.2
Day 14: 12 Hours	n	6	6	6	6	6	5	12
	Mean	5.83	8.08	3.04	2.43	0.85	0.97	6.09
	Min, Max	1.5, 10.2	3.5, 18.9	0.6, 5.0	0.6, 4.2	0.2, 2.3	0.2, 2.7	3.2, 11.5
		Presumptive NAFLD						
Day 1: Baseline	n	6	6	6	6	6	6	12
	Mean	17.08	13.71	12.95	23.71	15.08	13.39	18.59
	Min, Max	3.2, 47.0	2.9, 26.1	4.0, 22.7	1.1, 94.5	4.8, 31.8	4.5, 31.0	3.7, 85.9
Day 14: 12 Hours	n	6	6	6	6	6	6	12
	Mean	4.61	5.88	3.11	1.78	0.71	0.24	9.92
	Min, Max	2.3, 10.5	1.3, 12.9	0.8, 5.6	0.2, 4.5	0.3, 1.7	0.1, 0.4	3.7, 31.4

Pharmacodynamics

Figure 8. Plasma FGF19 at Day14: Plot of Mean (±SD) FGF19 vs Time in HV and PN



- Increases of FGF19 6-h post dose at D14 were observed demonstrating strong FXR target engagement (Figure 8)
- All EDP-305 doses showed increases in FGF19 levels as a % change from Baseline vs PBO in PN, while doses ≥ 2.5mg in HV showed similar effects (Table 5)

Table 5: Mean Percent Change from BL in Plasma FGF19 6H post-dose at Day 14 in HV and PN

		Healthy Volunteers							Presumptive NAFLD						
Visit/ Timepoint	Statistic	EDP-305 0.5 mg (N=6)	EDP-305 1 mg (N=6)	EDP-305 2.5 mg (N=6)	EDP-305 5 mg (N=6)	EDP-305 10 mg (N=6)	EDP-305 20 mg (N=6)	Placebo (N=12)	EDP-305 0.5 mg (N=6)	EDP-305 1 mg (N=6)	EDP-305 2.5 mg (N=6)	EDP-305 5 mg (N=6)	EDP-305 10 mg (N=6)	EDP-305 20 mg (N=6)	Placebo (N=12)
Day 1: BL	n	6	6	6	6	6	6	12	6	6	6	6	6	5	6	12
	Mean	89.22	158.28	124.55	77.40	126.5	110.93	135.28	99.9	88.0	87.60	97.33	140	148	147
	Min, Max	76.1, 121	51.7, 427.6	27.5, 408	46.1, 105.4	30.2, 321	38.8, 193	36.8, 749.3	31.3, 168.5	53.4, 164	34.6, 234	50.1, 246	44.9, 287.4	37.4, 354	24.9, 405
Day 14: 6 H	n	6	6	6	6	6	3	10	6	6	4	6	4	6	11
	Mean	303.58	383.91	1738.6	1029.28	749	592.15	481.01	588	431	1160	1578.5	786	4095	215
	Min, Max	48.7, 644	-57.2, 1450	94.7, 5012	263, 2395	243, 1544	17.8, 1366	-65.1, 1707	16.9, 1560	-39.8, 886	547, 2114	537, 3376	237, 2048	380, 11438	-17.3, 634

Conclusion

- EDP-305 was generally safe over a broad range of single and multiple doses with PK suitable for once daily oral dosing.
- Overall PK/PD profiles were similar between HV and PN, with a more pronounced PD effect in PN than HV at all doses when compared to PBO
- Significant elevations of FGF19 and diminutions in C4 demonstrated potent engagement of the FXR receptor at doses that neither elicit adverse effects on lipids nor result in itch
  - Phase 2 studies will be conducted including doses of EDP-305 in the 0.5 to 5 mg dose range