

# 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)

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## 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- $\alpha$ -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<sup>TM</sup> and dietary-induced NASH (DIN) mouse models

- Reduced liver fibrosis in multiple rodent models of fibrosis (e.g. Mdr2<sup>-/-</sup> mice, methionine- and choline-deficient diet, thioacetamide, and bile duct ligation)

## 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	Presumptive NAFLD								Overall (N=98)
	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)	6 (50.0)	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 (24,54)	36.7 (24,55)	36.7 (24,55)	36.7 (24,55)	36.7 (24,55)	36.7 (24,55)	35.4 (25,49)	36.2 (23,61)	
Mean BMI (range)	28.82 (23.6, 28.4)	23.72 (21.2, 26.2)	26.52 (21.2, 28.3)	27.62 (21.2, 29.5)	25.83 (21.2, 28.6)	27.97 (21.2, 29.3)	28.10 (26.2, 29.5)	26.07 (21.2, 29.5)	

## 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  $\geq$  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								Overall (N=48)
	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)	
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)	

- 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)

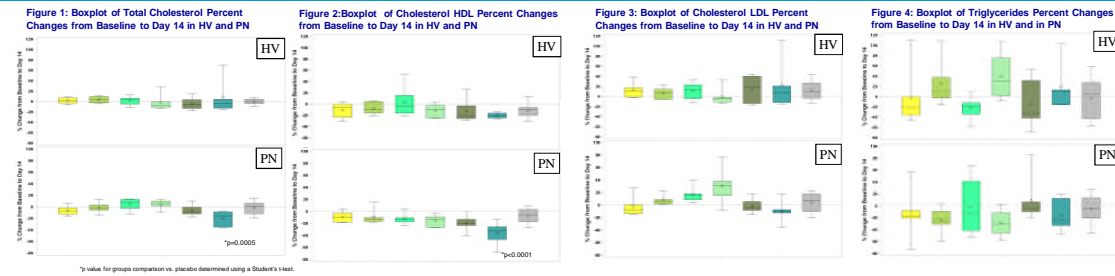
## Acknowledgments

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

## Disclosures

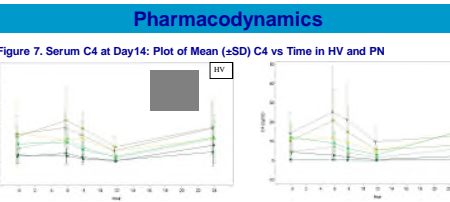
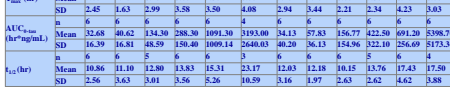
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## RESULTS



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

Study Population	Healthy Volunteers						Presumptive NAFLD					
	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)	Placebo (N=12)	
$C_{max}$ (ng/mL)	2.99	3.69	12.57	22.22	69.52	184.90	2.64	4.58	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	37.99	282.20
$T_{max}$ (hr)	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
$AUC_{0-\infty}$ (hr*ng/mL)	32.68	40.62	134.30	288.30	1091.30	1193.00	34.13	57.83	156.77	422.50	691.20	5398.70
SD	16.39	16.81	48.59	150.40	1009.14	2400.03	40.20	36.13	154.96	322.10	256.69	6173.36
$t_{1/2}$ (hr)	6	6	6	6	6	6	6	6	6	6	6	6
SD	3.56	3.63	3.01	3.56	3.26	10.59	3.16	3.97	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

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

Visit/Treatment	Healthy Volunteers								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)	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	Mean	7.88	12.50	24.54	26.68	26.42	25.60	6.12	Mean	19.57	27.24	36.96	16.08	51.87	45.42	84.52
Day 14: 12 Hours	Mean	5.83	8.08	3.04	2.43	0.85	0.97	6.09	Mean	115.10	35.18	86.58	66.42	82.23	82.27	32.11

## Pharmacokinetics

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

Visit/Treatment	Healthy Volunteers								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)	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	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	
Day 14: 6 Hours	Mean	76.1	121	517, 427.6	275, 408	461, 105.4	302, 321	388, 193	368, 749.3	313, 168.5	53.4, 164	346, 234	581, 246	449, 287.4	374, 354	249, 385

- Increases of FGF19 6h 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 HV, while doses  $\geq$  2.5mg in HV showed similar effects (Table 5)

## Conclusion

- EDP-305 was generally safe over a broad range of single and multiple doses with PK suitable for once daily dosing.
- Overall PK/PD profiles were similar between HV and PN, with a more pronounced PK 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