EDP-297: A Novel, Highly Potent, Farnesoid X Receptor Agonist: Results of a Phase 1 Study in Healthy Subjects

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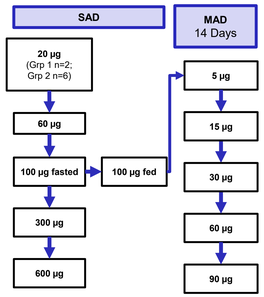
INTRODUCTION

EDP-297 is a potent FXR agonist under development for the treatment of non-alcoholic steatohepatitis (NASH). EDP-297 attenuates NASH-relevant pathways of steatosis, liver injury, inflammation, and apoptosis both *in vitro* and *in vivo*. Here, we present pharmacokinetic (PK), pharmacodynamic (PD), food effect (FE), and safety results of a single ascending dose (SAD) and multiple ascending dose (MAD) phase 1 study in healthy subjects (HS).

METHODS

Study Design:

A randomized, double-blind, placebo-controlled (PBO) study was conducted to evaluate the safety, tolerability, PK/ food effect, and PD of single and multiple doses of EDP-297 in healthy subjects. Subjects received EDP-297 as a single dose (SAD, 5 cohorts, 20-600 µg) or once daily (QD) for 14 days (MAD, 5 cohorts, 5-90 µg), (6 active: 2 PBO/cohort), except in the SAD FE cohort (8 active: 2 PBO). PD measurements included fibroblast growth factor 19 (FGF-19) and 7-a-hydroxy-4-cholesten-3-one (C4).



Key Objectives:

- Primary
  - To evaluate the safety and tolerability of single and multiple doses of EDP-297 administered to healthy subjects
- Secondary
  - To evaluate the pharmacokinetics (PK) of single and multiple doses of EDP-297 in both plasma and urine in healthy subjects
  - To evaluate the effect of food intake on PK of EDP-297 administered as a single dose in healthy subjects

Key Inclusion/Exclusion Criteria:

- Inclusion Criteria:
  - Male and female subjects of any ethnic origin between the ages of 18 and 65 years
  - Healthy on the basis of a medical evaluation
  - BMI of 18 to 30 kg/m^2 with a minimum body weight of 50 kg
- Exclusion Criteria:
  - Having high risk factors of contracting COVID-19
  - Pregnant or nursing females
  - Clinically relevant evidence or history of illness or disease
  - Positive urine drug screen at screening or Day -2
  - Current tobacco smokers or use of tobacco within 1 month prior to screening

Assessments:

- Safety and tolerability assessments evaluated throughout study conduct:
  - Adverse event monitoring, clinical laboratory, vital signs, physical examination, and electrocardiographic evaluations performed throughout study
  - Lipid profile
- PK and PD assessments
  - Intensive sampling after single doses over 24 hr for PK on Day 1 (including predose on Day 2), then at 30, 36, 48, 60, 72, 96, and 120 hr postdose
  - Intensive sampling after multiple doses over 24 hr for PK on Day 1 (including predose on Day 2) and over 96 hr on Day 14 (with additional samples in the morning on Days 15, 16, 17, and 18) and additional predose samples on Days 3, 4, 5, 6, 7, 8, 10, 11, 12, 13
  - PK parameters estimated using non-compartmental analysis
  - PD measurements included plasma fibroblast growth factor 19 (FGF-19) and serum 7-α-hydroxy-4-cholesten-3-one (C4): samples were collected on Day -1, Day 1, and Day 14 at predose, 1, 2, 3, 4, 6, 8, 12, 24 hr postdose

RESULTS

Subject Disposition and Demographics

- Demographics are summarized in Table 1 (SAD) and Table 2 (MAD)
- A total of 82 subjects (n=42 in SAD; n=40 in MAD) received at least one dose of EDP-297 or PBO
- **SAD**: all 10 placebo subjects completed the study; 2 out of 32 active subjects early terminated (n=1 in 100 µg cohort and n=1 in 600 µg cohort discontinued study due to COVID-19 related positive test and/or exposure)
- **MAD**: all 10 placebo subjects completed the study; 1 out of 30 active subjects early terminated (n=1 in 90 µg cohort discontinued study due to AE)

Table 1. Demographics, SAD Phase

	Pooled Placebo Fasted (N=10)	20 µg Fasted (N=6)	60 µg Fasted (N=6)	100 µg Fasted (N=8)	300 µg Fasted (N=6)	600 µg Fasted (N=6)	Placebo Fed (N=2)	100 µg Fed (N=7)	Overall (N=42)*
Age (years), mean (SD)	30.8 (13.05)	29.5 (16.74)	23.3 (7.34)	30.3 (11.02)	24.5 (3.33)	34.2 (20.61)	27.0 (7.07)	30.0 (11.87)	**29.0 (12.83)**
Male, n (%)	6 (60.0)	5 (83.3)	2 (33.3)	6 (75.0)	5 (83.3)	4 (66.7)	1 (50.0)	5 (71.4)	**28 (66.7)**
White, n (%)	8 (80.0)	4 (66.7)	3 (50.0)	4 (50.0)	5 (83.3)	5 (83.3)	1 (50.0)	3 (42.9)	**29 (69.0)**
Not Hispanic or Latino, n (%)	10 (100)	6 (100)	5 (83.3)	8 (100)	6 (100)	6 (100)	2 (100)	7 (100)	**41 (97.6)**
BMI (kg/m^2)[a]	23.15 (2.912)	23.53 (4.396)	22.48 (2.199)	25.84 (2.849)	24.07 (2.582)	23.28 (3.752)	20.90 (1.697)	25.40 (2.771)	**23.77 (3.154)**
Weight (kg), mean (SD)	71.04 (7.479)	72.15 (8.377)	60.42 (5.517)	78.48 (14.350)	77.15 (14.380)	71.23 (11.102)	69.10 (1.980)	76.59 (14.385)	**72.00 (11.488)**

Unique subjects with Fasted/Fed subjects counted only once

Table 2. Demographics, MAD Phase

	Pooled Placebo Fasted (N=10)	5 µg Fasted (N=6)	15 µg Fasted (N=6)	30 µg Fasted (N=6)	60 µg Fasted (N=6)	90 µg Fasted (N=6)	Overall (N=40)
Age (years), mean (SD)	41.3 (16.37)	37.2 (13.75)	36.7 (13.66)	42.3 (12.09)	26.7 (4.84)	32.7 (17.81)	**36.7 (14.17)**
Male, n (%)	9 (90.0)	5 (83.3)	5 (83.3)	4 (66.7)	5 (83.3)	6 (100)	**34(85.0)**
White, n (%)	8 (80.0)	4 (66.7)	4 (66.7)	4 (66.7)	6 (100)	4 (66.7)	**30 (75.0)**
Not Hispanic or Latino, n (%)	8 (80.0)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	**38 (95.0)**
BMI (kg/m^2)[a]	25.41 (3.727)	25.03 (1.450)	24.05 (4.026)	22.90 (2.153)	23.12 (2.401)	23.07 (3.020)	**24.08 (3.027)**
Weight (kg), mean (SD)	76.71 (12.797)	79.38 (7.705)	75.80 (6.887)	73.82 (9.654)	76.62 (11.478)	74.10 (14.845)	**76.13 (10.574)**

Pharmacokinetics

- PK data is summarized in Figure 1/Table 3 (SAD) and Figure 2/Table 4 (MAD)
- Data is supportive of once daily dosing with a mean $t_{1/2}$ following multiple doses of EDP-297 of ~9-12.5 hours
- As the dose increased, exposures increased in a dose proportional manner in the SAD phase and Day 1 MAD, and an approximately dose proportional manner on Day 14 (MAD) (Figure 1, Figure 2)
- No food effect was observed
- For multiple doses of EDP-297 ≤60 µg, accumulation ratio was 1.3-2.3, and 5-fold for 90 µg, although the higher accumulation at 90 µg was not associated with PK characteristics or half-life changes
- Urine PK (SAD only) showed EDP-297 and metabolites were generally not quantifiable in urine at any dose

Figure 1. Mean Plasma Concentration by Cohort (SAD)

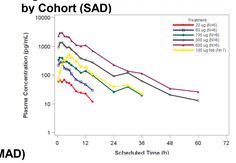


Figure 2. Mean Plasma Concentration by Cohort (MAD)

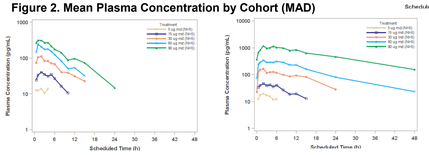


Table 3. EDP-297 Plasma PK Parameters SAD (fasted)[c]

PK Parameters	20 µg (N=6)	60 µg (N=6)	100 µg (N=8)	100 µg fed (N=7)[c]	300 µg (N=6)	600 µg (N=6)
$AUC_{0\text{-}inf}$ (pg/mL*hr)[a]	739 (39.8)	1980 (18.6)	4070 (37.7)	4880 (43.3)	13000 (33.4)	28900 (34.1)
C_{max} (pg/mL)[a]	76.3 (25.2)	298 (31.0)	456 (33.4)	531 (31.4)	1520 (22.7)	3520 (24.8)
T_{max} (hr)[b]	2.5 (0.5-3.1)	2.0 (0.5-2.0)	1.0 (0.5-2.0)	5.0 (5.0 – 8.1)	2.0 (1.0-3.0)	1.5 (0.5-3.0)
$T_{1/2}$ (hr)[a]	8.38 (30.6)	6.54 (58.0)	9.29 (47.8)	8.78 (28.1)	10.2 (19.5)	8.13 (30.2)

a. Data presented as Geometric Mean (Geometric %CV)
b. Data presented as Median (Range)
c. All cohorts were dosed in the fasted state except for 100 µg fed cohort

Table 4. EDP-297 Day 14 Plasma PK Parameters MAD (fasted)

PK Parameters	5 µg QD (N=6)	15 µg QD (N=6)	30 µg QD (N=6)	60 µg QD (N=6)	90 µg QD (N=6)
$AUC_{0\text{-}24}$ (pg/mL*hr)[a]	241 (36.0)	515 (20.2)	1830 (52.1)	3990 (81.6)	14900 (79.9)
C_{max} (pg/mL)[a]	19.2 (27.2)	51.9 (13.0)	185 (28.2)	375 (39.4)	1060 (63.0)
T_{max} (hr)[b]	2.0 (1.0-4.0)	2.0 (0.5-6.0)	2.0 (0.5-5.0)	2.0 (0.5-8.0)	2.0 (2.0-8.0)
$T_{1/2}$ (hr)[a]	8.62 (53.8)	8.73 (36.9)	8.51 (41.3)	9.11 (44.9)	12.5 (23.9)
Accumulation Ratio[c]	1.34 (23.8)	1.50 (16.9)	1.86 (52.2)	2.28 (62.4)	5.34 (61.0)

a. Data presented as Geometric Mean (Geometric %CV)
b. Data presented as Median (Range)
c. Accumulation Ratio based on $AUC_{0\text{-}24}$

Pharmacodynamics – MAD

- C4 and FGF-19 are displayed in Figure 3 and 4, respectively. Table 5 shows % change from baseline for C4 and FGF-19 for both Day 1 and 14
- C4 Mean $AUC_{0\text{-}24}$ decreased as the doses of EDP-297 were increased, with ≥50% target engagement for multiple doses of 30 µg and higher, and up to a 91.7% decrease from baseline was observed at the highest multiple dose of 90 µg
- C4 Mean C_{min} decreased as the doses of EDP-297 were increased, with ≥50% target engagement for multiple doses of 30 µg and higher, and up to a 95.1% decrease from baseline was observed at the highest multiple dose of 90 µg
- The two lowest MAD doses (5, 15 µg) were not associated with pruritus, and resulted in modest C4 target engagement (<50%)
- FGF-19 $AUC_{0\text{-}24}$ generally increased as doses of EDP-297 were increased, with 94.7% increase from baseline observed at the highest multiple dose of 90 µg
- FGF-19 C_{max} did not show clear dose response as EDP-297 doses were increased, with 64.5% increase from baseline observed at multiple doses of 15 µg

Figure 3. C4 Arithmetic Mean PD-Time Profiles Absolute Values (MAD)

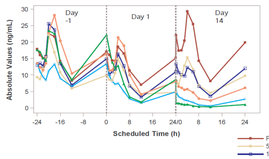


Figure 4. FGF-19 Arithmetic Mean PD-Time Profiles Absolute Values (MAD)

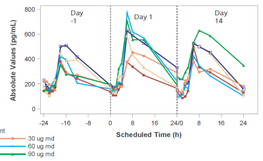


Table 5. % Change from Baseline in C4 and FGF-19 Mean (SD) (MAD)

Dose (µg)	Day 1				Day 14			
	C4		FGF-19		C4		FGF-19	
	C_{min}	$AUC_{(0\text{-}24)}$	C_{max}	$AUC_{(0\text{-}24)}$	C_{min}	$AUC_{(0\text{-}24)}$	C_{max}	$AUC_{(0\text{-}24)}$
Placebo	-2.7 (24.4)	-14.6 (16.2)	16.9 (32.8)	12.9 (28.2)	32.8 (72.0)	32.4 (68.3)	35.0 (45.2)	18.8 (40.2)
5	-26.3 (12.3)	-33.5 (9.1)	21.0 (19.0)	1.0 (12.8)	-21.0 (25.4)	-9.3 (40.6)	22.4 (12.6)	12.0 (27.7)
15	-48.1 (8.0)	-35.2 (20.2)	75.8 (146.0)	30.4 (16.0)	-38.5 (32.8)	-20.7 (50.2)	64.5 (154.2)	-1.3 (19.8)
30	**-54.9 (13.4)**	**-41.2 (13.6)**	**32.7 (19.2)**	**39.3 (10.3)**	**-76.0 (8.5)**	**-72.5 (14.3)**	**3.3 (48.4)**	**7.3 (53.9)**
60	**-68.4 (9.3)**	**-55.0 (7.7)**	**78.8 (37.4)**	**90.9 (37.0)**	**-87.8 (15.9)**	**-76.5 (18.3)**	**-0.1 (38.2)**	**0.8 (27.5)**
90	**-75.9 (8.1)**	**-56.8 (6.7)**	**62.4 (43.2)**	**85.0 (64.9)**	**-95.1 (8.1)**	**-91.7 (7.2)**	**36.3 (41.8)**	**94.7 (113.2)**

Safety

Figure 5. Mean Change from Baseline in Total Cholesterol Concentration-Time (MAD)

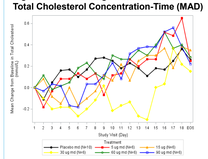


Figure 6. Mean Change from Baseline in HDL Concentration-Time (MAD)

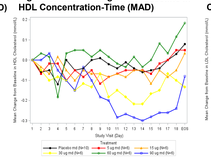


Figure 7. Mean Change from Baseline in LDL Concentration-Time (MAD)

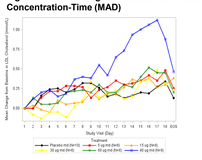


Figure 8. Mean Change from Baseline in Triglyceride Concentration-Time (MAD)

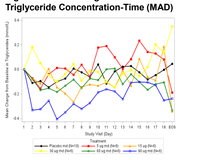


Table 6. Summary of TEAEs by Preferred Term (PT) in ≥2 subjects in any arm (SAD)

System Organ Class Preferred Term [n (%)]	Pooled Placebo Fasted (N=10)	20 µg Fasted (N=6)	60 µg Fasted (N=6)	100 µg Fasted (N=8)	300 µg Fasted (N=6)	600 µg Fasted (N=6)	Placebo Fed (N=2)	100 µg Fed (N=7)
Total Subjects with at least one TEAE	7 (70)	4 (66.7)	2 (33.3)	4 (50.0)	5 (83.3)	5 (83.3)	2 (100.0)	2 (28.6)
Nervous system disorders								
Headache	1 (10.0)	0	0	0	2 (33.3)	1 (16.7)	0	0
Dizziness	0	0	0	0	2 (33.3)	0	0	0
General disorders and administration site conditions								
Haematoma	0	0	0	0	2 (33.3)	0	0	0
Musculoskeletal and connective tissue disorder								
Myalgia	1 (10.0)	2 (33.3)	1 (16.7)	0	1 (16.7)	0	0	0
Respiratory, thoracic and mediastinal disorders								
Dyspnoea	2 (20.0)	0	0	0	0	0	0	0
Skin and subcutaneous tissue disorders								
Pruritus	1 (10.0)	0	0	0	2 (33.3)	2 (33.3)	0	0

TEAE = Treatment-Emergent Adverse Event; N=number of subjects exposed; n = number of subjects %=number of subjects (n) as a percentage of number of subjects (N) per treatment

Table 7. Summary of TEAEs by Preferred Term (PT) in ≥2 subjects in any arm (MAD)

System Organ Class Preferred Term [n (%)]	Pooled Placebo Fasted (N=10)	5 µg QD Fasted (N=6)	15 µg QD Fasted (N=6)	30 µg QD Fasted (N=6)	60 µg QD Fasted (N=6)	90 µg QD Fasted (N=6)
Total Subjects with at least one TEAE	7 (70.0)	3 (50.0)	4 (66.7)	6 (100.0)	6 (100.0)	6 (100.0)
Gastrointestinal disorders						
Abdominal Discomfort	1 (10.0)	0	0	3 (50.0)	1 (16.7)	1 (16.7)
Nervous system disorders						
Headache	0	1 (16.7)	1 (16.7)	4 (66.7)	2 (33.3)	1 (16.7)
General disorders and administration site conditions						
Fatigue	2 (20.0)	0	0	0	1 (16.7)	0
Catheter Site Related Reaction	2 (20.0)	0	0	3 (50.0)	0	1 (16.7)
Vessel Puncture Site Thrombosis	0	0	0	0	2 (33.3)	0
Medical Device Site Reaction	0	0	0	2 (33.3)	1 (16.7)	0
Musculoskeletal and connective tissue disorder						
Arthralgia	0	0	0	2 (33.3)	0	0
Skin and subcutaneous tissue disorders						
Pruritus	2 (20.0)	0	0	1 (16.7)	2 (33.3)	4 (66.7)
Dry Skin	2 (20.0)	0	0	0	3 (50.0)	0

TEAE = Treatment-Emergent Adverse Event; N=number of subjects exposed; n = number of subjects. %=number of subjects (n) as a percentage of number of subjects (N) per treatment.

- EDP-297 was generally well tolerated following single and multiple doses for 14 days. No SAEs or discontinuations due to TEAEs in SAD (up to 600 µg) and MAD (up to 60 µg). Most TEAEs were mild and were not related/unlikely related to study drug (Table 6, 7)
- In the SAD phase, all TEAEs were mild except for 5 subjects with Grade 2 events: n=1 headache (placebo), n=1 myalgia (20 µg), n=3 (300 µg) , where n=1 headache, dizziness, syncope, and n=2 pruritus
- In the MAD phase, all TEAEs were mild except for 5 subjects: n=1 moderate pruritis (30 µg) and n=4 severe pruritis (90 µg)
- Pruritus was observed at single doses ≥300 µg and multiple doses ≥30 µg with n=1 D/C due to pruritus in the highest MAD cohort (90 µg)
- There were no clinically significant abnormal safety laboratory or abnormal ECG findings, except for n=1 Grade 2 ALT elevation (MAD 90 µg) that was not associated with other liver enzyme abnormalities
- There were no clinically meaningful changes in the lipid profile, except for a trend towards decrease in HDL and increase in LDL at MAD 90 µg; and mean lipids values were within normal range during the entire study (Figures 5-8)

CONCLUSIONS

- EDP-297, a potent and selective FXR agonist, was safe and well tolerated with PK suitable for once daily oral dosing, a strong target engagement, and no food effect
- Overall EDP-297 was well tolerated except for pruritus and liver enzyme elevations observed especially at highest MAD dose (90 µg)
  - Pruritus was observed at single doses ≥300 µg and multiple doses ≥30 µg with one discontinuation in the highest MAD cohort (90 µg)
  - One subject in the highest MAD cohort 90 µg experienced a G2 ALT elevation that was not associated with other changes in liver enzymes
- EDP-297 exposure increased with increasing single and multiple doses, with time-linear pharmacokinetics, and a half-life supporting once daily dosing, and no food effect was observed
- Strong FXR target engagement was demonstrated, following multiple doses, with increase in FGF-19 and decrease in C4 up to 95% and 92%, respectively

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DISCLOSURES

AA, CM, NA, EL are employees of Enanta Pharamceuticals. JO and SM are employees of PRA-ICON