A Phase 2 dose ranging, randomized, double-blind and placebo-controlled study of EDP-305 in subjects with non-alcoholic steatohepatitis (NASH)

Topline Results

September 25, 2019
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EDP-305
A Novel, Potent FXR Agonist

• NASH is considered the fastest-growing cause of cirrhosis, hepatocellular carcinoma and indication for liver transplantation

• EDP-305 is a potent, non-bile acid FXR receptor agonist \(^{[1-4]}\)
  - Improvement in hepatocyte ballooning and overall NAFLD Activity Score (NAS) in the STAM\(^{\text{TM}}\) and dietary-induced NASH (DIN) mouse models
  - Reduced liver fibrosis in multiple rodent models of fibrosis
    • Mdr2\(^{-/-}\) mice, methionine- and choline-deficient diet, thioacetamide, and bile duct ligation

• In a 2-week Phase 1 study, EDP-305 was generally safe over a broad range of single and multiple doses with PK suitable for once daily oral dosing \(^{[5]}\)
  - Doses were identified with significant target engagement of the FXR receptor that neither elicited adverse effects on lipids nor resulted in pruritus
  - >400 subjects exposed to EDP-305 across the entire program

• Fast Track Designation granted by FDA
ARGON-1 Study Design

- The primary objectives of the study were as follows:
  - To evaluate change in ALT levels at Week 12
  - To evaluate the safety and tolerability of EDP-305

- Key secondary objectives included:
  - Change in liver fat by MRI-PDFF
  - Change in lipids
  - Pharmacokinetics
  - Pharmacodynamic parameters: C4 and FGF19
Key Eligibility Criteria

**Key Inclusion Criteria**

- Histologic evidence on a historical liver biopsy within 24 months of screening consistent with NASH with fibrosis (no cirrhosis), and elevated ALT at screening

OR

- Phenotypic diagnosis of NASH based on elevated ALT ($\geq 50$ IU/L and $\leq 200$ IU/L) and diagnosis of type 2 diabetes mellitus (T2DM)

  AND

- Screening MRI-PDFF with $>8\%$ steatosis

**Key Exclusion Criteria**

- Evidence of other chronic disease
- Any histology or clinical evidence of cirrhosis
- HbA1c $\geq 9\%$
- Prior use of OCA
- Use of a new statin regimen
- Use of a new antidiabetic regimen
- Significant alcohol consumption

NASH: non-alcoholic steatohepatitis; ALT: alanine aminotransferase; MRI-PDFF: magnetic resonance imaging-proton density fat fraction; HbA1c: hemoglobin A1c; OCA: obeticholic acid
ARGON-1: Subject Disposition
Efficacy Population, N=132

500 Screened

366 excluded

134 Randomized (R)

n=1 R but not dosed

24 Placebo
4 Disc Treatment
- 2 AE
- 1 LTFU
- 1 Withdrew

20 with both BL and W12 ALT

n=1 R but not dosed

55 EDP-305 1mg
6 Disc Treatment
- 1 AE
- 1 LTFU
- 2 Withdraw
- 1 PD
- 1 Stopping Rule

48* with both BL and W12 ALT

53 EDP-305 2.5mg
14 Disc Treatment
- 12 AE
- 1 LTFU
- 1 Withdrew

38* with both BL and W12 ALT

* n=1 in each arm with value assessed outside of visit window
R: randomized; Disc: discontinued; AE: adverse event; LTFU: lost to follow-up; BL: baseline; ALT: alanine aminotransferase
# Demographic and Baseline Characteristics

**Efficacy Population**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo N=24</th>
<th>EDP-305 1 mg N=55</th>
<th>EDP-305 2.5 mg N=53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>50.8 (10.5)</td>
<td>51.5 (12.0)</td>
<td>52.3 (11.8)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>11 (45.8%)</td>
<td>29 (52.7%)</td>
<td>29 (54.7%)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>17 (70.8%)</td>
<td>42 (76.4%)</td>
<td>47 (88.7%)</td>
</tr>
<tr>
<td>Hispanic/Latino, n (%)</td>
<td>11 (45.8%)</td>
<td>22 (40.0%)</td>
<td>26 (49.1%)</td>
</tr>
<tr>
<td>BMI (kg/m^2), mean (SD)</td>
<td>36.1 (5.5)</td>
<td>34.5 (4.9)</td>
<td>33.8 (5.3)</td>
</tr>
<tr>
<td>ALT (U/L), mean (SD)</td>
<td>78.5 (22.2)</td>
<td>91.9 (35.5)</td>
<td>79.5 (25.8)</td>
</tr>
<tr>
<td>AST (U/L), mean (SD)</td>
<td>55.3 (29.2)</td>
<td>53.3 (24.9)</td>
<td>54.9 (29.2)</td>
</tr>
<tr>
<td>MRI-PDFF (%), mean (SD)</td>
<td>20.3 (8.7)</td>
<td>22.1 (7.6)</td>
<td>19.0 (7.9)</td>
</tr>
</tbody>
</table>

**Concomitant medication use**

<table>
<thead>
<tr>
<th>Type</th>
<th>Placebo N=24</th>
<th>EDP-305 1 mg N=55</th>
<th>EDP-305 2.5 mg N=53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidiabetic</td>
<td>19 (79.2%)</td>
<td>39 (70.9%)</td>
<td>32 (60.4%)</td>
</tr>
<tr>
<td>Metformin</td>
<td>17 (70.8%)</td>
<td>35 (63.6%)</td>
<td>30 (56.6%)</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>1 (4.2%)</td>
<td>0</td>
<td>3 (5.7%)</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>0</td>
<td>6 (10.9%)</td>
<td>4 (7.5%)</td>
</tr>
<tr>
<td>Antilipidemic</td>
<td>9 (37.5%)</td>
<td>25 (45.5%)</td>
<td>17 (32.1%)</td>
</tr>
</tbody>
</table>

SD: standard deviation
ALT (U/L) Change at Week 12 - Efficacy Population

- Primary Endpoint Was Met in the 2.5mg Arm
- Numerically Higher Reduction with 1mg Compared to Placebo

LS Mean Change (SE)

SE: standard error

ALT (U/L)

Absolute Change from Baseline

- Placebo (N=20)  
- EDP-305 1mg (N=48)  
- EDP-305 2.5mg (N=38)

p=0.049
Proportion of Subjects with an Absolute Reduction in ALT (U/L) at Week 12
Efficacy Population

Percentage of Subjects with a Reduction

<table>
<thead>
<tr>
<th>Absolute Change from Baseline (ALT)</th>
<th>Placebo (N=20)</th>
<th>EDP-305 1.0mg (N=48)</th>
<th>EDP-305 2.5mg (N=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;20 (U/L)</td>
<td>35</td>
<td>52.1</td>
<td>60.5</td>
</tr>
<tr>
<td>&gt;25 (U/L)</td>
<td>20</td>
<td>45.8</td>
<td>44.7</td>
</tr>
<tr>
<td>&gt;30 (U/L)</td>
<td>20</td>
<td>39.6</td>
<td>36.8</td>
</tr>
</tbody>
</table>
MRI-PDFF Absolute Change From Baseline at Week 12 Efficacy Population

Key Secondary Endpoint Was Met in the 2.5mg Arm

-2.4
-3.3
-7.1

SE: standard error

MRI-PDFF (%) Absolute Change from Baseline

Placebo (N=20) EDP-305 1mg (N=51) EDP-305 2.5mg (N=49)

p<0.001
MRI-PDFF Percent Change From Baseline at Week 12
Efficacy Population
Key Secondary Endpoint Was Met in the 2.5mg Arm

MRI-PDFF (%)
Percent Change from Baseline

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Change (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (N=20)</td>
<td>-11.9 (SE)</td>
</tr>
<tr>
<td>EDP-305 1mg (N=51)</td>
<td>-15.3 (SE)</td>
</tr>
<tr>
<td>EDP-305 2.5mg (N=49)</td>
<td>-30.5 (SE)</td>
</tr>
</tbody>
</table>

SE: standard error
p=0.007

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Proportion of Subjects with Relative Change From Baseline (Absolute and Percent) in Liver Fat Reduction (%) at Week 12 Efficacy Population

<table>
<thead>
<tr>
<th>MRI-PDFF (%) (&gt;=5) Absolute Change from Baseline</th>
<th>MRI-PDFF (%) (&gt;=30%) Percent Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (N=20)</td>
<td>EDP-305 1mg (N=51)</td>
</tr>
<tr>
<td>20</td>
<td>31.4</td>
</tr>
<tr>
<td>25</td>
<td>25.5</td>
</tr>
</tbody>
</table>
Mean Change in ALT by MRI-PDFF Response at Week 12
Efficacy Population

ALT (U/L) Mean Change

MRI-PDFF >=30% reduction  MRI-PDFF <30% reduction

-15.9 -31.8 -35.3  
-13.2 -21.1 -17.9

Placebo (N=20)  EDP-305 1mg (N=48)  EDP-305 2.5mg (N=38)
Percentage Change in C4 and FGF19 (Pre-dose) at Week 12 - Efficacy Population

C4 (nmol/L)

FGF19 (ng/L)

SE: standard error

EDP 305-101 TOPLINE RESULTS
Response in Markers of Liver Injury and Target Engagement (ALP) Efficacy Population

ALT (U/L) vs. Weeks

AST (U/L) vs. Weeks

GGT (U/L) vs. Weeks

ALP (U/L) vs. Weeks

SE: standard error

Placebo (N=24) | EDP-305 1mg (N=55) | EDP-305 2.5mg (N=53)
Summary of Treatment-Emergent Adverse Events
Safety Population

<table>
<thead>
<tr>
<th>Subjects, n (%)</th>
<th>Placebo N=24</th>
<th>EDP-305 1mg N=55</th>
<th>EDP-305 2.5mg N=53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects with any TEAE</td>
<td>12 (50.0%)</td>
<td>32 (58.2%)</td>
<td>39 (73.6%)</td>
</tr>
<tr>
<td>• Subjects with any Severe TEAE</td>
<td>3 (12.5%)</td>
<td>2 (3.6%)</td>
<td>2 (3.8%)</td>
</tr>
<tr>
<td>• Subjects with any Serious TEAE</td>
<td>1 (4.2%)</td>
<td>1 (1.8%)</td>
<td>0</td>
</tr>
<tr>
<td>• Subjects with any TEAE Leading to Study Drug Discontinuation</td>
<td>2 (8.3%)</td>
<td>1 (1.8%)</td>
<td>12 (22.6%)</td>
</tr>
<tr>
<td>• Pruritus generalized</td>
<td>0</td>
<td>1 (1.8%)</td>
<td>11 (20.8%)</td>
</tr>
<tr>
<td>• Rash</td>
<td>0</td>
<td>0</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>• Vomiting</td>
<td>1 (4.2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>• Cerebrovascular accident</td>
<td>1 (4.2%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- TEAEs were mostly mild to moderate in severity
- Severe TEAEs were more frequent in placebo arm
- No SAEs occurred in EDP-305 2.5mg arm
- Majority of discontinuations occurred in EDP-305 2.5mg arm
  - All were due to moderate pruritus (=11) or moderate rash (n=1)

TEAE: treatment-emergent adverse event
## Most Frequent Treatment-Emergent Adverse Events
### Events Occurring in ≥ 5% of Subjects in Any Treatment Arm
### Safety Population

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo N=24</th>
<th>EDP-305 1mg N=55</th>
<th>EDP-305 2.5mg N=53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus generalized</td>
<td>1 (4.2%)</td>
<td>5 (9.1%)</td>
<td>25 (47.2%)</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>1 (1.8%)</td>
<td>4&lt;sup&gt;a&lt;/sup&gt; (7.5%)</td>
</tr>
<tr>
<td>Pruritus&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1 (4.2%)</td>
<td>0</td>
<td>3&lt;sup&gt;b&lt;/sup&gt; (5.7%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (4.2%)</td>
<td>3 (5.5%)</td>
<td>2 (3.8%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>2 (3.6%)</td>
<td>3 (5.7%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (8.3%)</td>
<td>1 (1.8%)</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0</td>
<td>3 (5.5%)</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (8.3%)</td>
<td>2 (3.6%)</td>
<td>2 (3.8%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (4.2%)</td>
<td>3 (5.5%)</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>0</td>
<td>3 (5.5%)</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>Cough</td>
<td>0</td>
<td>1 (1.8%)</td>
<td>3 (5.7%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (8.3%)</td>
<td>2 (3.6%)</td>
<td>2 (3.8%)</td>
</tr>
</tbody>
</table>

- Most frequent TEAEs were mild to moderate in severity
- TEAEs are consistent with the observed safety profile of EDP-305 in >400 subjects exposed to the drug to date

<sup>a</sup> Three of the 4 subjects are also counted in pruritus generalized
<sup>b</sup> Two of the 3 subjects reported intermittent local and generalized pruritus and are also counted in pruritus generalized
<sup>c</sup> Localized
Lipid Values (mg/dL) Over Time
Efficacy Population

Triglycerides (mg/dL)

Cholesterol (mg/dL)

HDL (mg/dL)

LDL (mg/dL)

LS Mean Change (SE)

LS Mean Change (SE)

LS Mean Change (SE)

LS Mean Change (SE)

Weeks

Weeks

Weeks

Weeks

0 D3 2 4 8 12
0 D3 2 4 8 12
0 D3 2 4 8 12
0 D3 2 4 8 12

Placebo (N=24) EDP-305 1mg (N=55) EDP-305 2.5mg (N=53)

SE: standard error

EDP 305-101 TOPLINE RESULTS
Summary of ARGON-1 Study
Efficacy

Primary (ALT change) and key secondary (MRI-PDFF) endpoints were met at week 12

• EDP-305 2.5mg achieved statistically significant ALT change
  - Mean reduction of ~28 U/L vs. 15 U/L in pbo group (p<0.05)
  - Numerically higher reduction with 1mg (~22 U/L) vs. pbo

• A statistically significant reduction in liver fat by MRI-PDFF with EDP-305 2.5mg (p<0.001)
  - 45% of subjects were MRI-PDFF responders (i.e. ≥30% fat reduction)

• EDP-305 exhibited strong target engagement as shown by reductions in C4, and increases in FGF-19 and ALP
  - Robust reduction in marker of liver injury, GGT
Summary of ARGON-1 Study
Safety and Tolerability

• EDP-305 regimens were generally safe in patients with NASH for up to 12 weeks with the majority of TEAEs being mild to moderate
  - The most common (≥5%) TEAEs included pruritus, GI related symptoms (nausea, vomiting, diarrhea), headache and dizziness
  - Consistent safety profile observed in >400 subjects exposed to EDP-305 up to 12 weeks
  - Incidence of treatment discontinuation due to pruritus was 1.8% for 1mg and 20.8% for 2.5mg

• Treatment with EDP-305 was associated with a small numeric absolute changes in lipids at week 12 relative to baseline
Next Steps

- Progress EDP-305 into a Ph2b NASH study called ARGON-2
  - Randomized, placebo-controlled in liver biopsy-proven NASH patients
  - 72-week treatment duration

Currently planning two doses versus placebo:

- Dose 1 (TBD) is designed to push for maximal efficacy in terms of histologic improvement
  - Based on ARGON-1, we expect to see some pruritus at this dose, but we also expect it to be manageable in the majority of these patients

- Dose 2 (TBD) is designed to offer a balanced profile in terms of efficacy and tolerability
  - Potential dose to explore in combinations for NASH while ARGON-2 is ongoing
We extend our thanks to the subjects who participated in this study, the Investigators and the site personnel for their conduct of the study.
References


5. 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, Kristin Sanderson, Daniel Dickerson, Nathalie Adda. NASH TAG 2018, Park City, Utah (poster #4) & EASL 2018, Paris, France (poster # FRI-489)
From Chemistry to Cures