E NANTA Pharmaceuticals

A Phase 2 Dose Ranging, Randomized, Double-blind and Placebo-Controlled Study of EDP-305 in Subjects With Non-Alcoholic Steatohepatitis (NASH)

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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
 - 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
 - *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
 - 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

 <u>Histologic evidence of NASH with</u> <u>fibrosis</u> on a historical liver biopsy within 24 months of screening, and elevated ALT¹ at screening

OR

 <u>Phenotypic diagnosis of NASH</u> based on **elevated ALT**¹ and diagnosis of type 2 diabetes mellitus (T2DM)

AND

- Screening MRI-PDFF with >8 % steatosis
- $^{1} \ge 50 \text{ IU/L}$ and $\le 200 \text{ IU/L}$

Key Exclusion Criteria

- Evidence of other chronic disease
- Any histology or clinical evidence of cirrhosis
- HbA1c ≥ 9%
- Prior use of OCA
- Initiation of a statin regimen for subjects not currently on stable dose
- Initiation of antidiabetic regimen for subjects not currently on stable dose
- 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, * alcohol consumption exceeding 14 drinks/week for females and 21 drinks/week for males within 6 months of Screening



Demographic and Baseline Characteristics ITT Population

| Characteristics | Placebo N=24 | EDP-305 1 mg N=55 | EDP-305 2.5 mg N=53 | |
|----------------------------------|-----------------|----------------------|------------------------|--|
| Age (years), mean (SD) | 50.8 (10.5) | 51.5 (12.0) | 52.3 (11.8) | |
| Female, n (%) | 11 (45.8%) | 29 (52.7%) | 29 (54.7%) | |
| White, n (%) | 17 (70.8%) | 42 (76.4%) | 47 (88.7%) | |
| Hispanic/Latino, n (%) | 11 (45.8%) | 22 (40.0%) | 26 (49.1%) | |
| BMI (kg/m²), mean (SD) | 36.1 (5.5) | 34.5 (4.9) | 33.8 (5.3) | |
| ALT (U/L), mean (SD) | 78.5 (22.2) | 91.9 (35.5) | 79.5 (25.8) | |
| AST (U/L), mean (SD) | 55.3 (29.2) | 53.3 (24.9) | 54.9 (29.2) | |
| MRI-PDFF (%), mean (SD) | 20.3 (8.7) | 22.1 (7.6) | 19.0 (7.9) | |
| Concomitant medication use, n(%) | | | | |
| Antidiabetic agents: | 19 (79.2%) | 39 (70.9%) | 32 (60.4%) | |
| Metformin | 17 (70.8%) | 35 (63.6%) | 30 (56.6%) | |
| Pioglitazone | 1 (4.2%) | 0 | 3 (5.7%) | |
| Vitamin E | 0 | 6 (10.9%) | 4 (7.5%) | |
| Lipid lowering agents | 9 (37.5%) | 25 (45.5%) | 17 (32.1%) | |

SD: standard deviation



ALT (U/L) Change at Week 12 - ITT Population

Primary Endpoint Was Met in the 2.5mg Arm

Pharmaceuticals

Numerically Higher Reduction with 1mg Compared to Placebo



MRI-PDFF Absolute Change From Baseline at Week 12 ITT Population Key Secondary Endpoint Was Met in the 2.5mg Arm





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





Mean Change in ALT by MRI-PDFF Response at Week 12 ITT Population





Response in Markers of Liver Injury and Target Engagement (ALP) ITT Population



SE: standard error



Percentage Change in C4 and FGF19 (Pre-dose) at Week 12 - ITT Population





Most Frequent Treatment-Emergent Adverse Events Events Occurring in ≥ 5% of Subjects in Any Treatment Arm Safety Population

| N (%) | Placebo N=24 | EDP-305 1mg N=55 | EDP-305 2.5mg N=53 |
|-------------------------|-----------------|---------------------|-----------------------|
| Pruritus generalized | 1 (4.2%) | 5 (9.1%) | 25 (47.2%) |
| Rash | 0 | 1 (1.8%) | 4 ^a (7.5%) |
| Pruritus ^c | 1 (4.2%) | 0 | 3 ^b (5.7%) |
| Nausea | 1 (4.2%) | 3 (5.5%) | 2 (3.8%) |
| Diarrhea | 0 | 2 (3.6%) | 3 (5.7%) |
| Vomiting | 2 (8.3%) | 1 (1.8%) | 1 (1.9%) |
| Urinary tract infection | 0 | 3 (5.5%) | 1 (1.9%) |
| Headache | 2 (8.3%) | 2 (3.6%) | 2 (3.8%) |
| Dizziness | 1 (4.2%) | 3 (5.5%) | 1 (1.9%) |
| Decreased appetite | 0 | 3 (5.5%) | 1 (1.9%) |
| Cough | 0 | 1 (1.8%) | 3 (5.7%) |
| Fatigue | 2 (8.3%) | 2 (3.6%) | 2 (3.8%) |

- Most frequent TEAEs were mild to moderate in severity
- Majority of discontinuations occurred in EDP-305 2.5mg arm (22.6%) compared to EDP-305 1mg arm (1.8%) and placebo (8.3%)
- SAEs: 1 in the placebo arm, and 1 in the EDP-305 1mg arm . No SAEs were reported in the 2.5 mg arm.

^a Three of the 4 subjects are also counted in pruritus generalized

^b Two of the 3 subjects reported intermittent local and generalized pruritus and are also counted in pruritus generalized



The Digital ILC 2020- August 28th

Lipid Values (mg/dL) Over Time ITT Population





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 Placebo group (p<0.05)
 - Numerically higher reduction with 1mg (~22 U/L) vs. Placebo
- 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 (≥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 accompanied by small numeric absolute changes in lipids at week 12 relative to baseline



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