ARGON-1

ENANTA 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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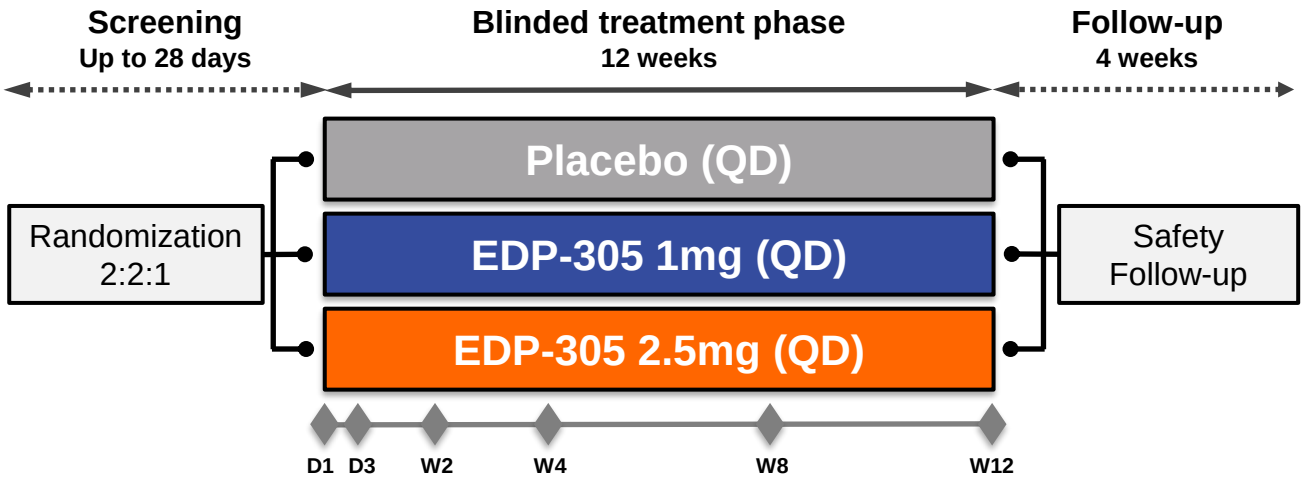
# Disclosures

- V Ratziu, M Rinella, B Tetri : consultancy for Enanta

# 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

- *Histologic evidence of NASH with fibrosis* on a historical liver biopsy within 24 months of screening, and **elevated ALT** [1] at screening

**OR**

- *Phenotypic diagnosis of NASH* based on **elevated ALT** [1] and diagnosis of type 2 diabetes mellitus (T2DM)

**AND**

- Screening MRI-PDFF with >8 % steatosis

[1] ≥ 50 IU/L and ≤ 200 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 ($kg/m^2$), 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%) |

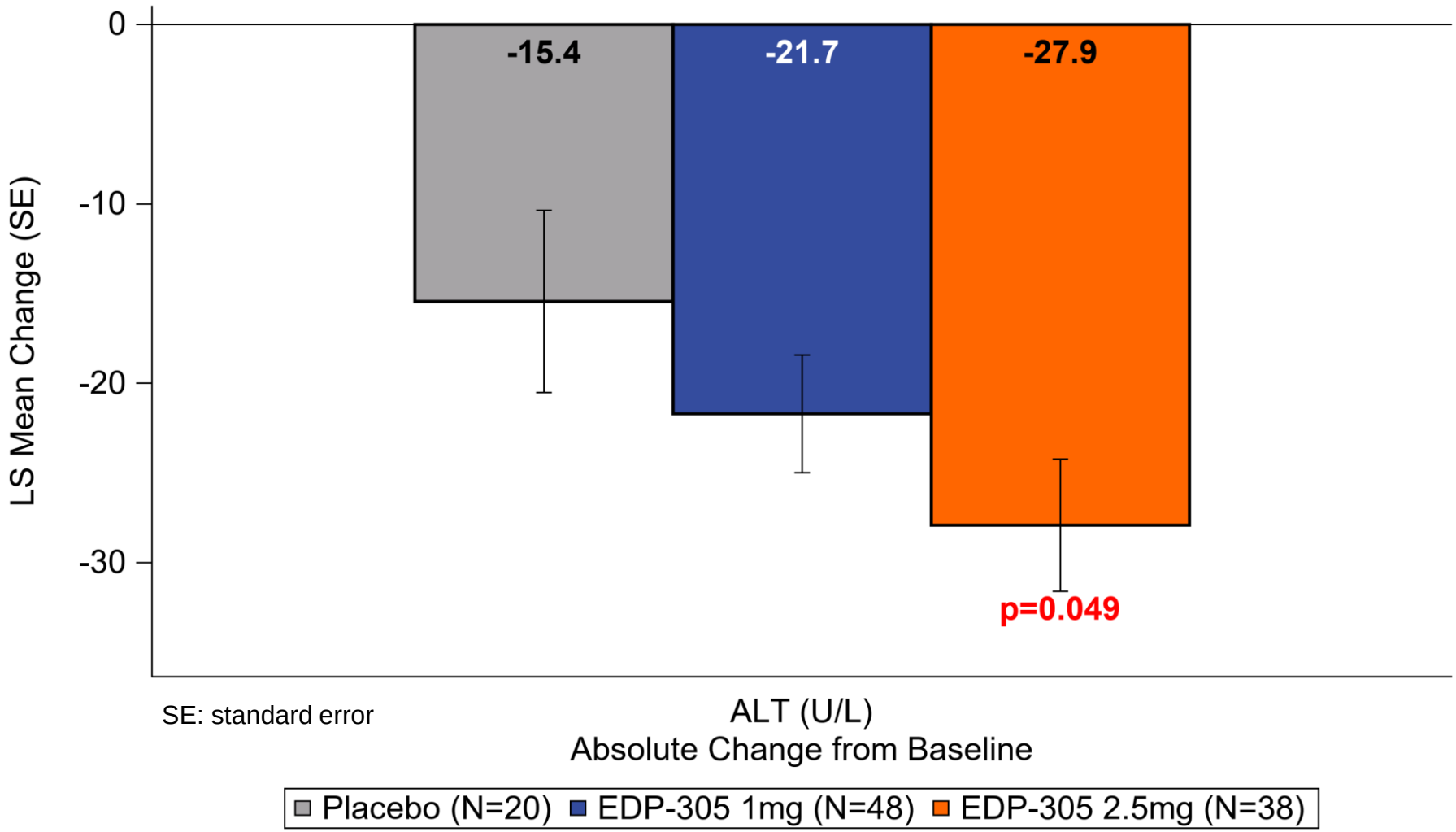
SD: standard deviation



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

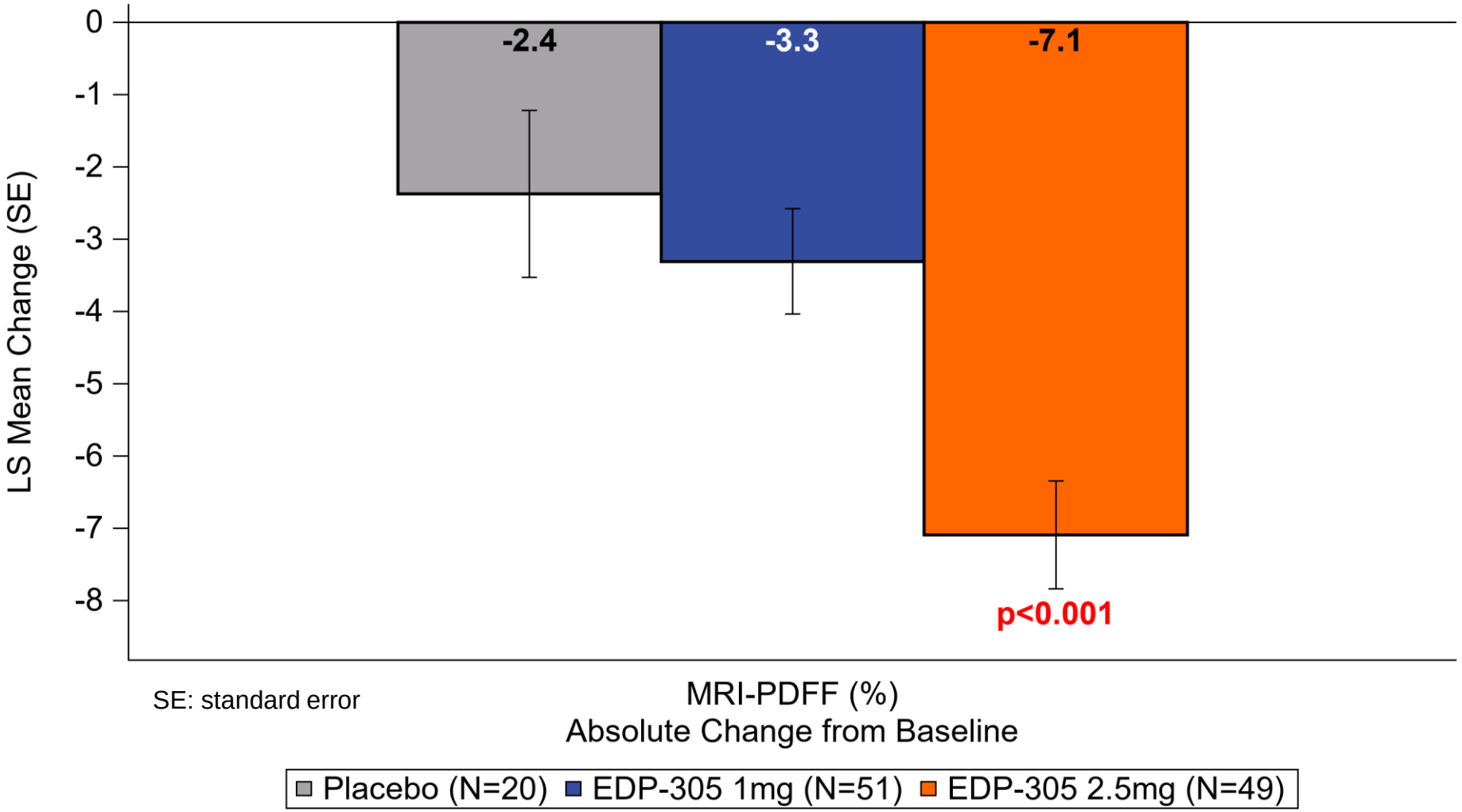
- **Primary Endpoint Was Met in the 2.5mg Arm**
- **Numerically Higher Reduction with 1mg Compared to Placebo**



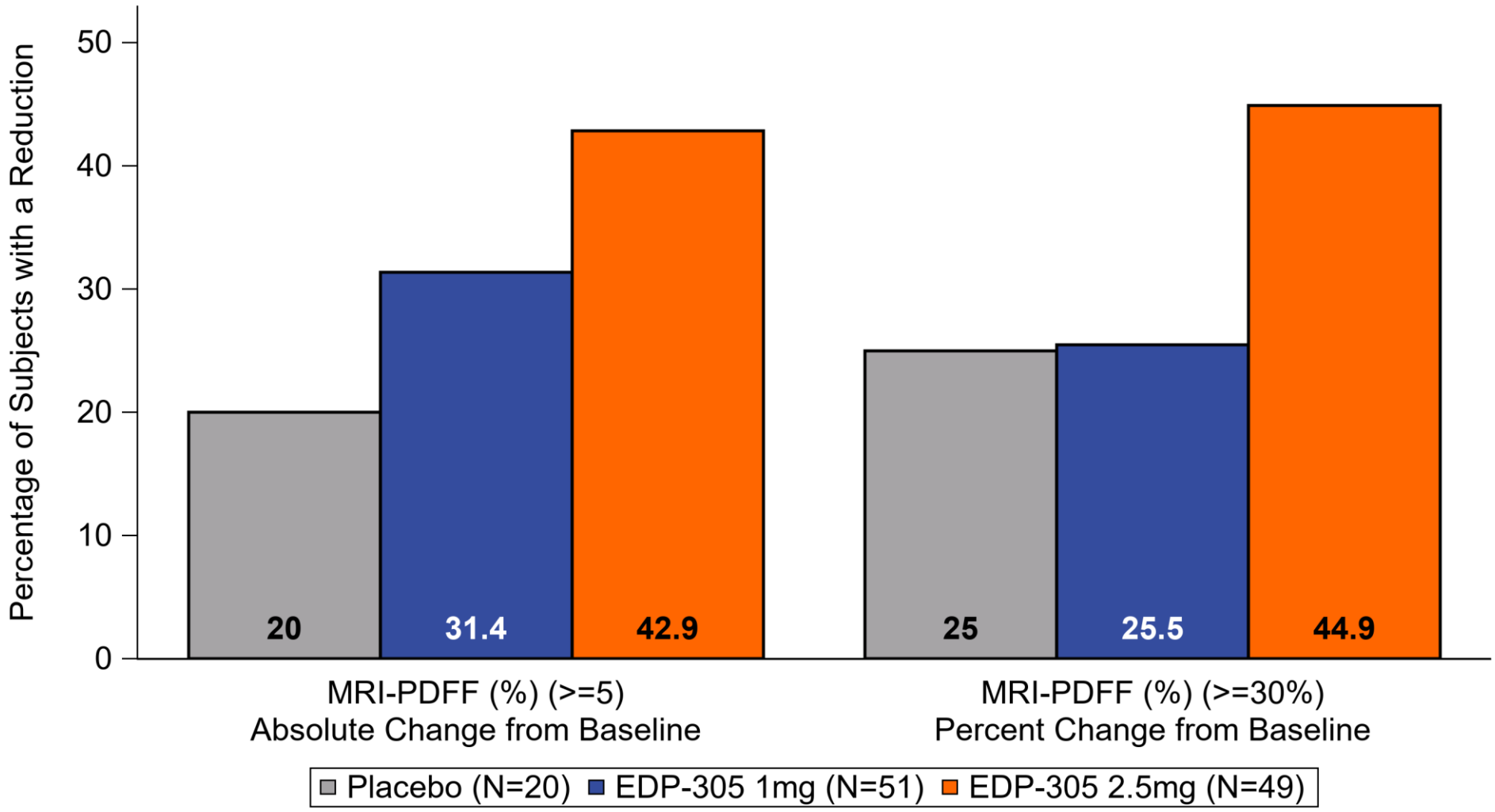


# MRI-PDFF Absolute Change From Baseline at Week 12
# ITT Population
## Key Secondary Endpoint Was Met in the 2.5mg Arm



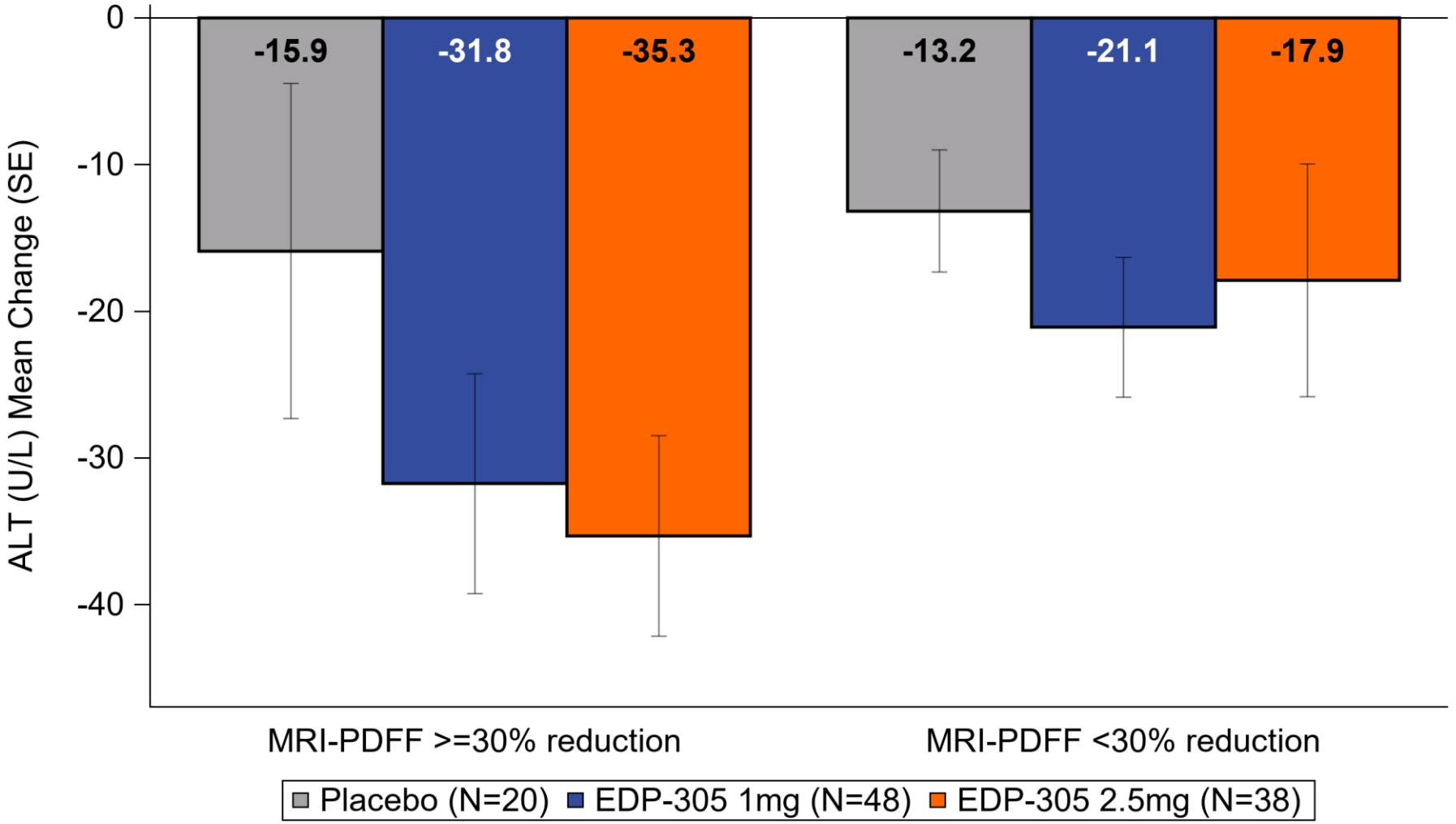
# Proportion of Subjects with Relative Change From Baseline (Absolute and Percent) in Liver Fat Reduction (%) at Week 12 ITT Population



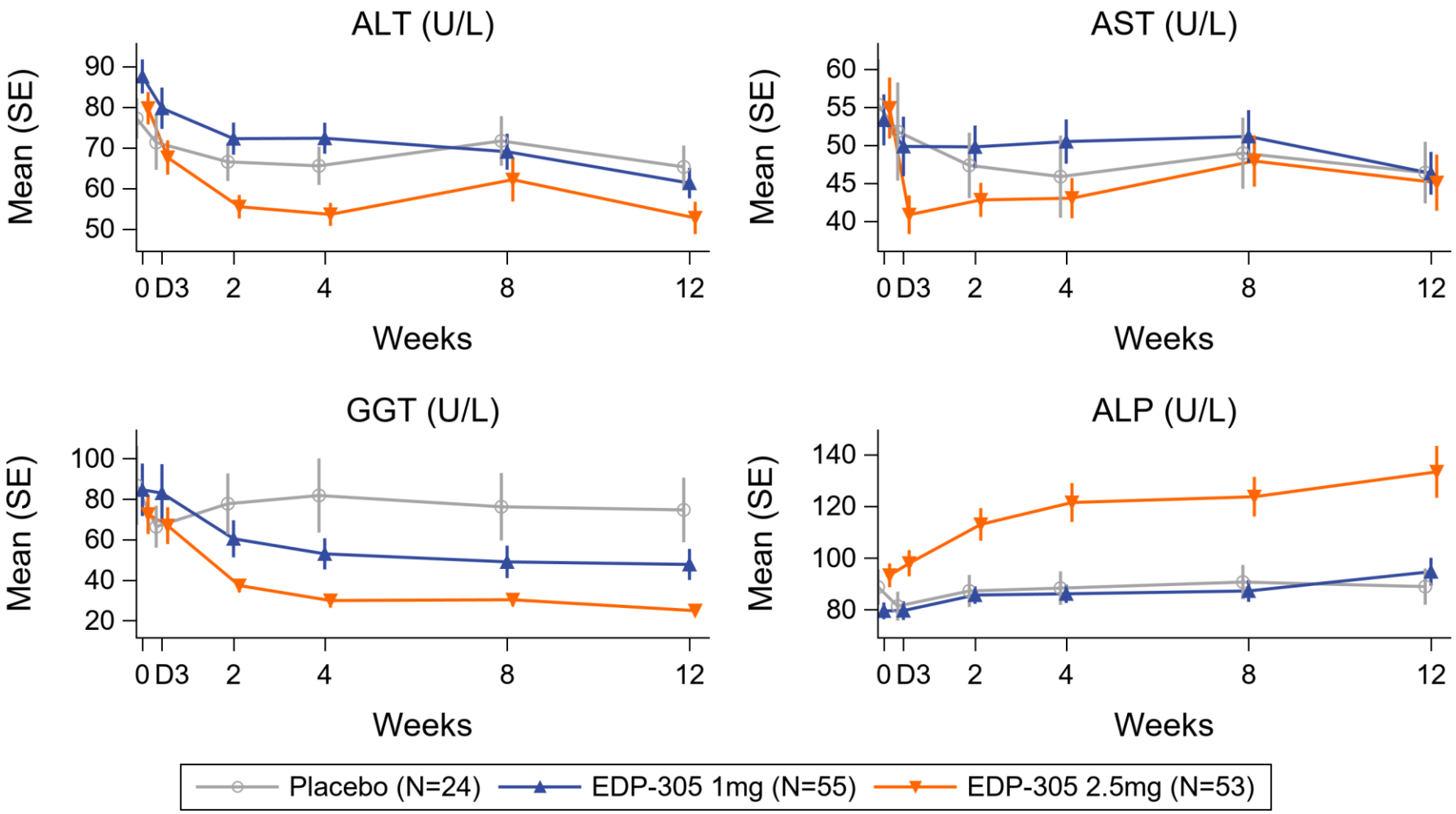


# Mean Change in ALT by MRI-PDFF Response at Week 12 ITT Population

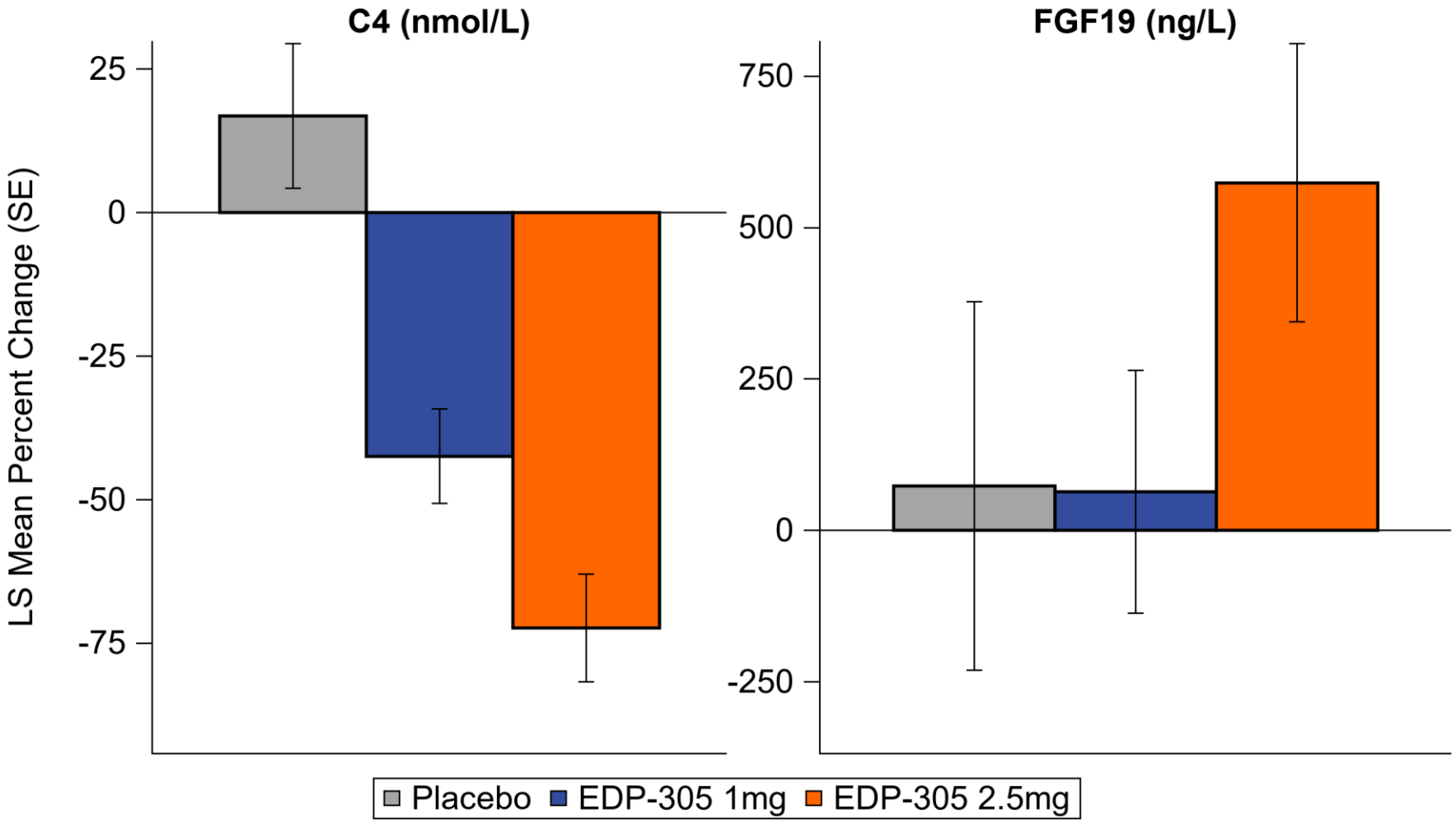


# Response in Markers of Liver Injury and Target Engagement (ALP)
# ITT Population




SE: standard error

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




SE: standard error

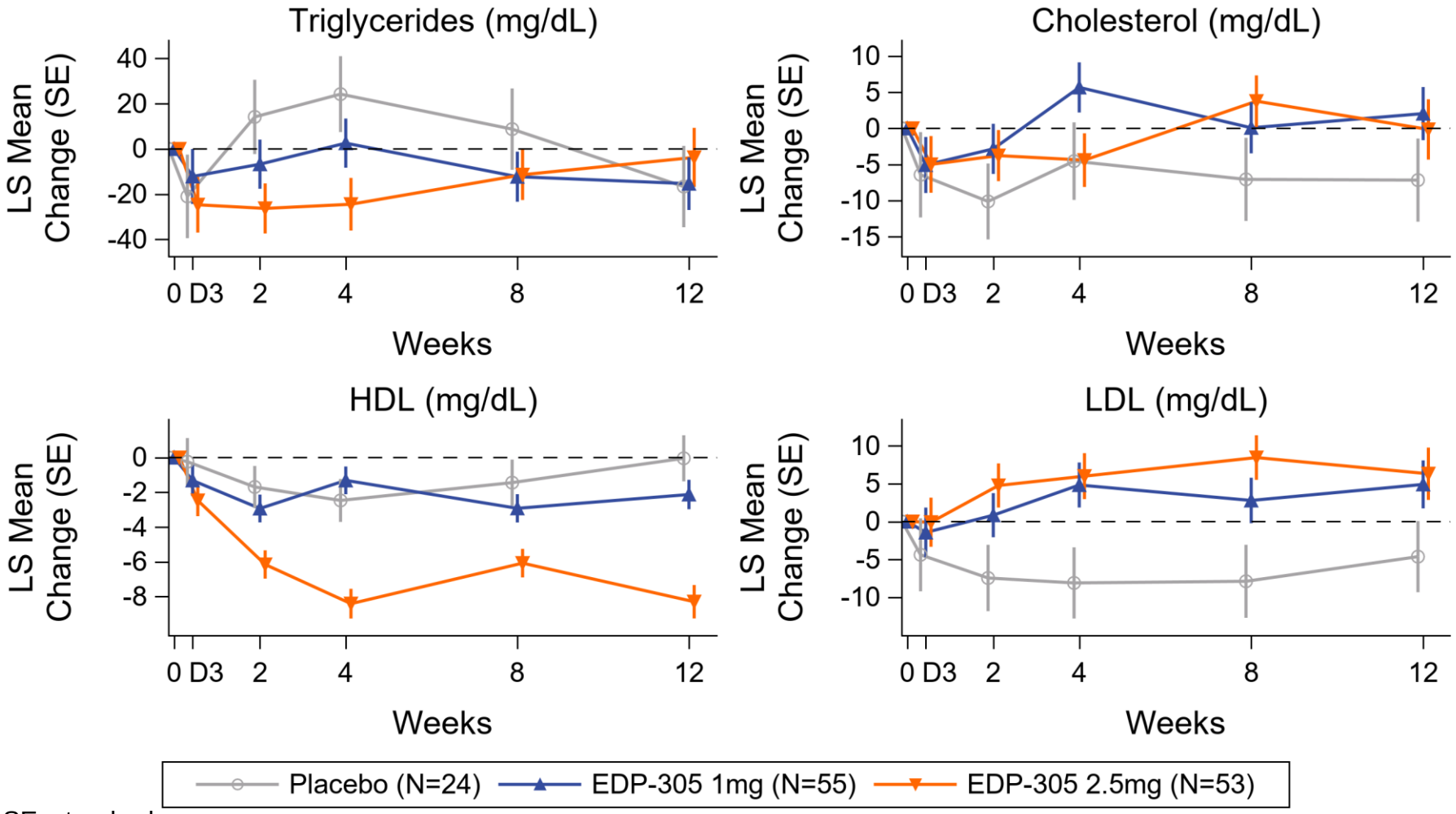
# Most Frequent Treatment-Emergent Adverse Events
## Events Occurring in ≥ 5% of Subjects in Any Treatment Arm
## Safety Population

| 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*
[c] *Localized*

# Lipid Values (mg/dL) Over Time
# ITT Population




SE: standard error

# 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

# Acknowledgments

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