

# ENANTA

## Pharmaceuticals

### ARGON-1

**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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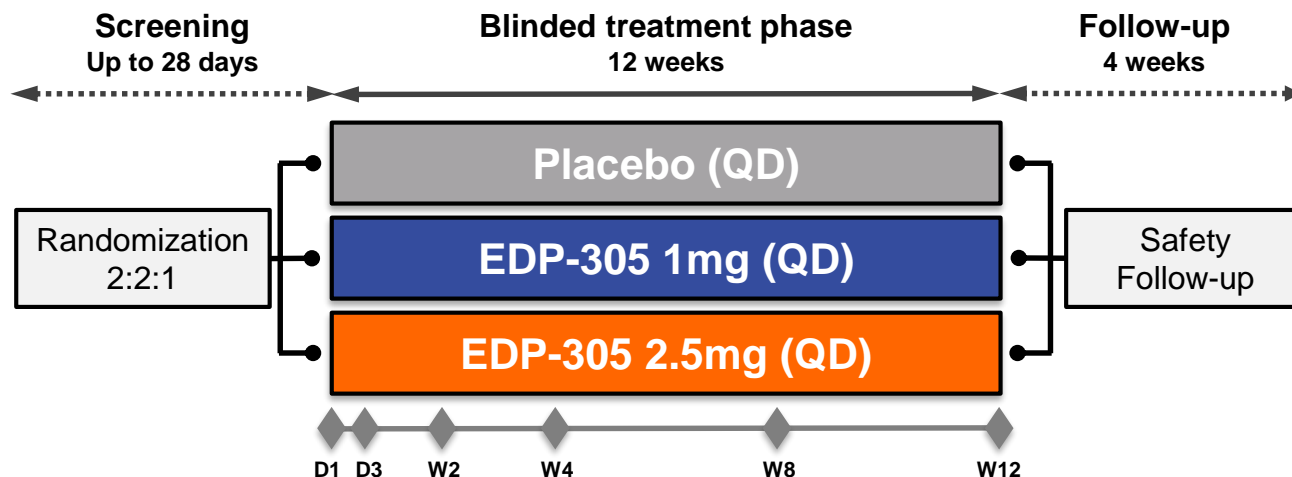
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# EDP-305

## 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 <sup>[1-4]</sup>
  - 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
    - *Mdr2*<sup>-/-</sup> 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 <sup>[5]</sup>
  - 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

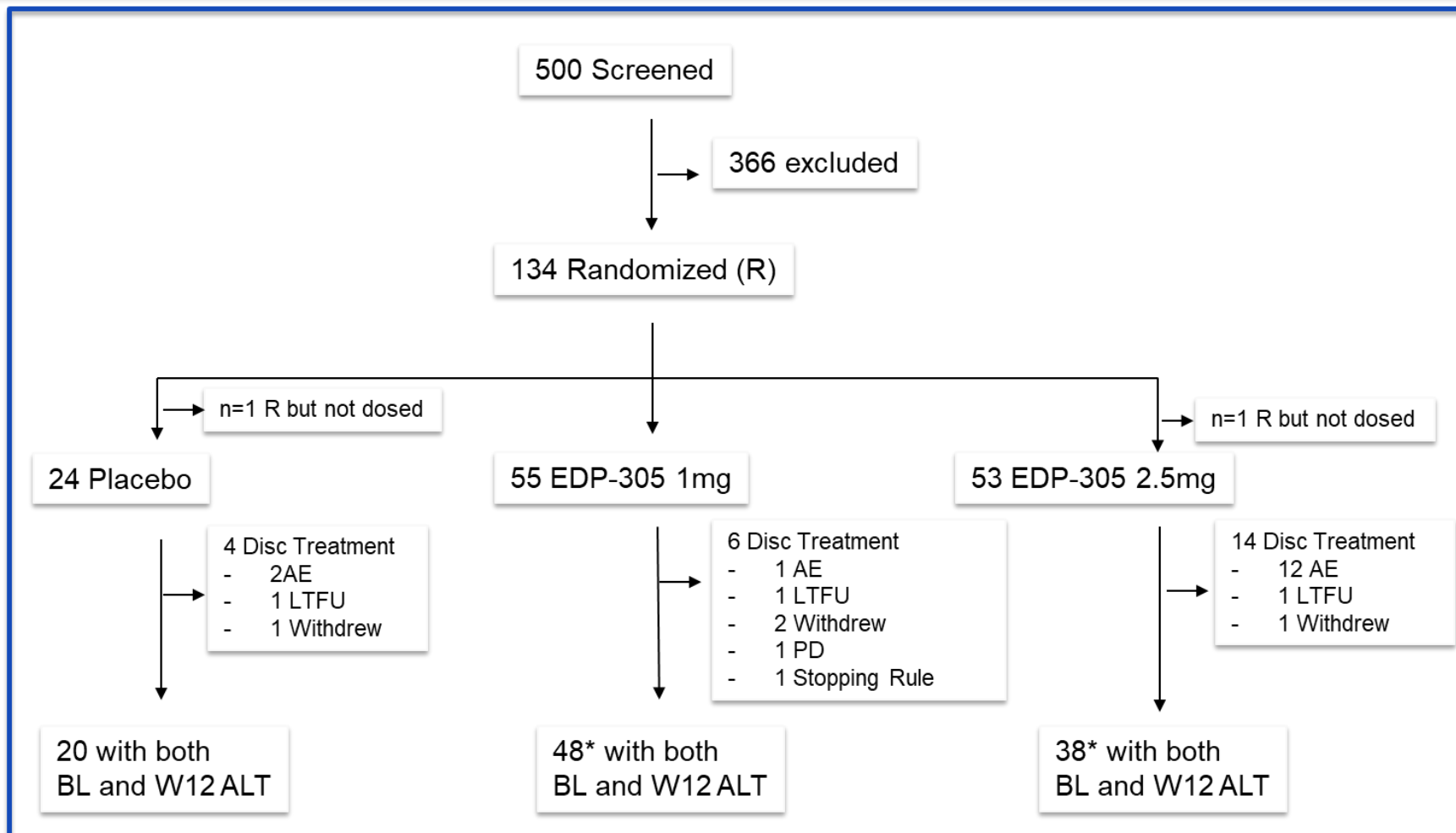
## Key Exclusion Criteria

- 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



\* 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

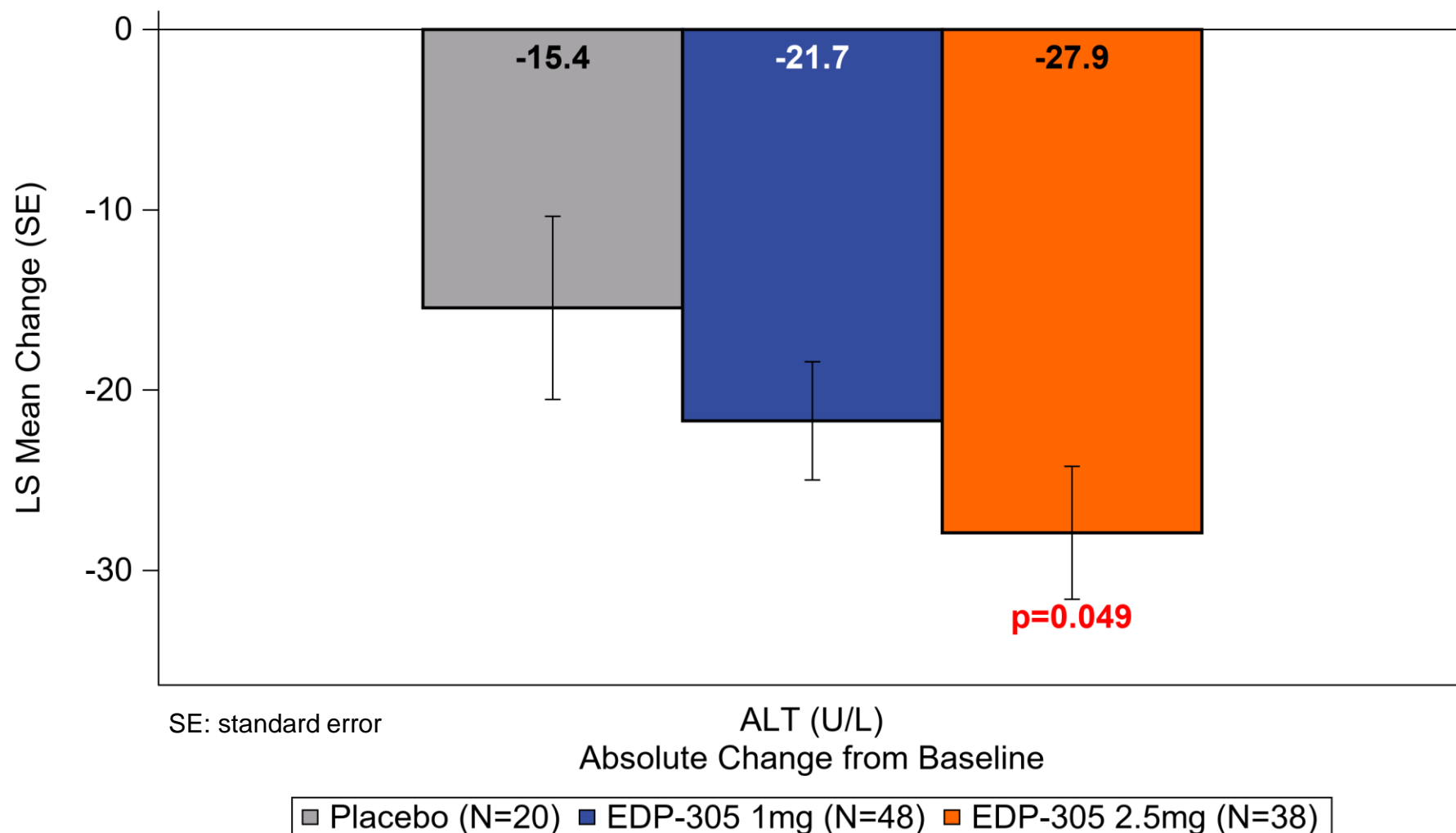
## Efficacy Population

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 <sup>2</sup> ), 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			
Antidiabetic	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%)
Antilipidemic	9 (37.5%)	25 (45.5%)	17 (32.1%)

SD: standard deviation

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

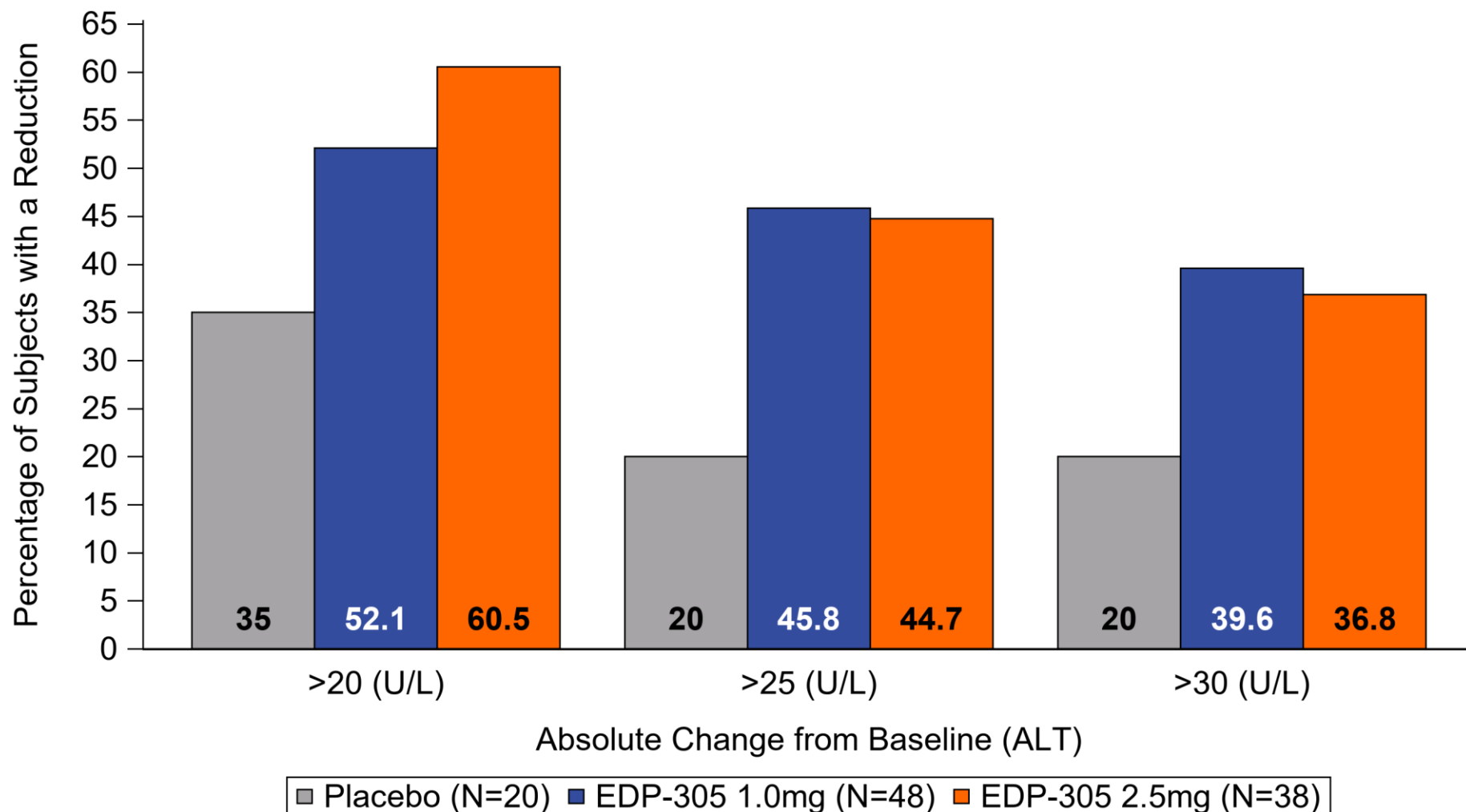
- **Primary Endpoint Was Met in the 2.5mg Arm**
- **Numerically Higher Reduction with 1mg Compared to Placebo**





# Proportion of Subjects with an Absolute Reduction in ALT (U/L) at Week 12

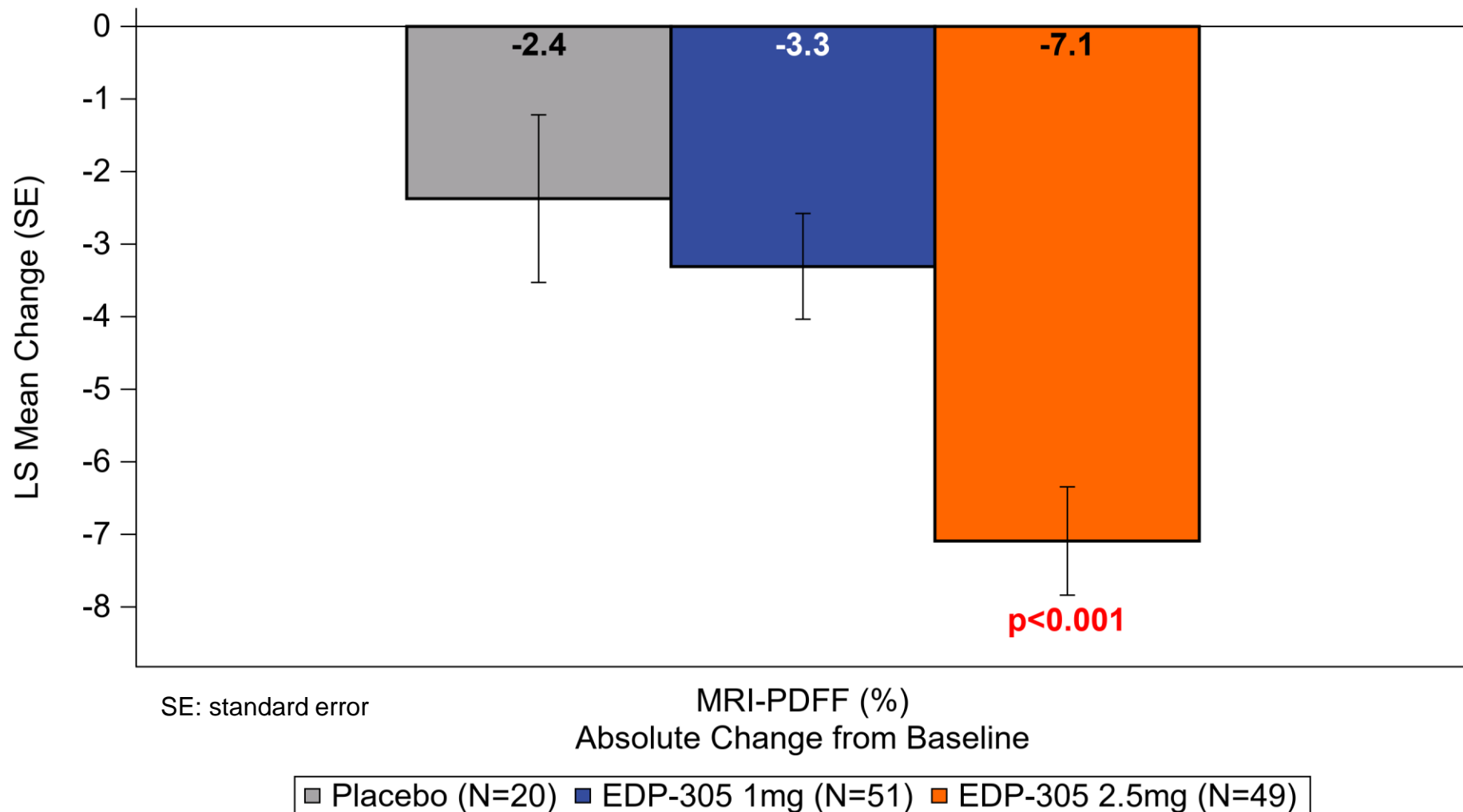
## Efficacy Population



# MRI-PDFF Absolute Change From Baseline at Week 12

## Efficacy Population

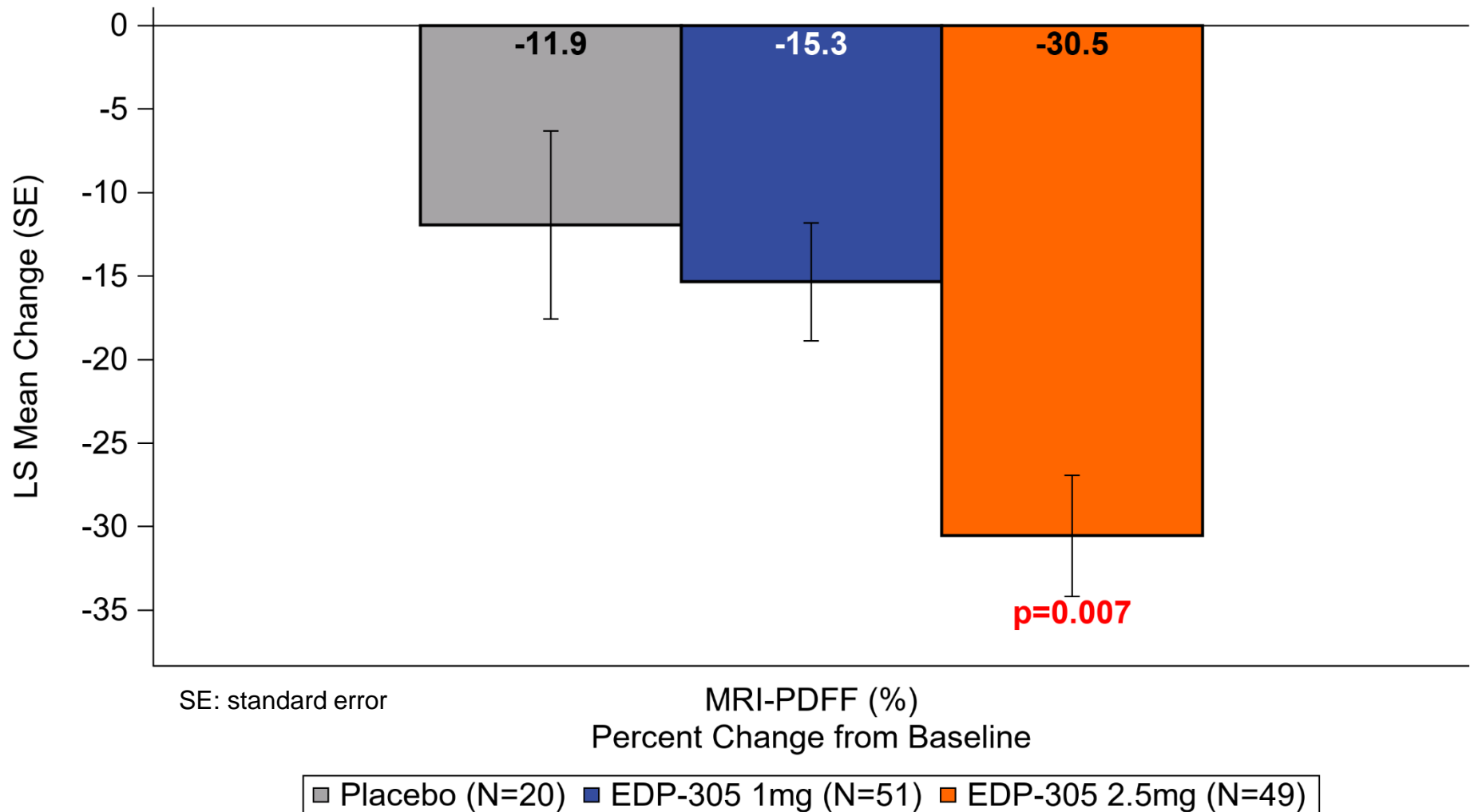
### Key Secondary Endpoint Was Met in the 2.5mg Arm



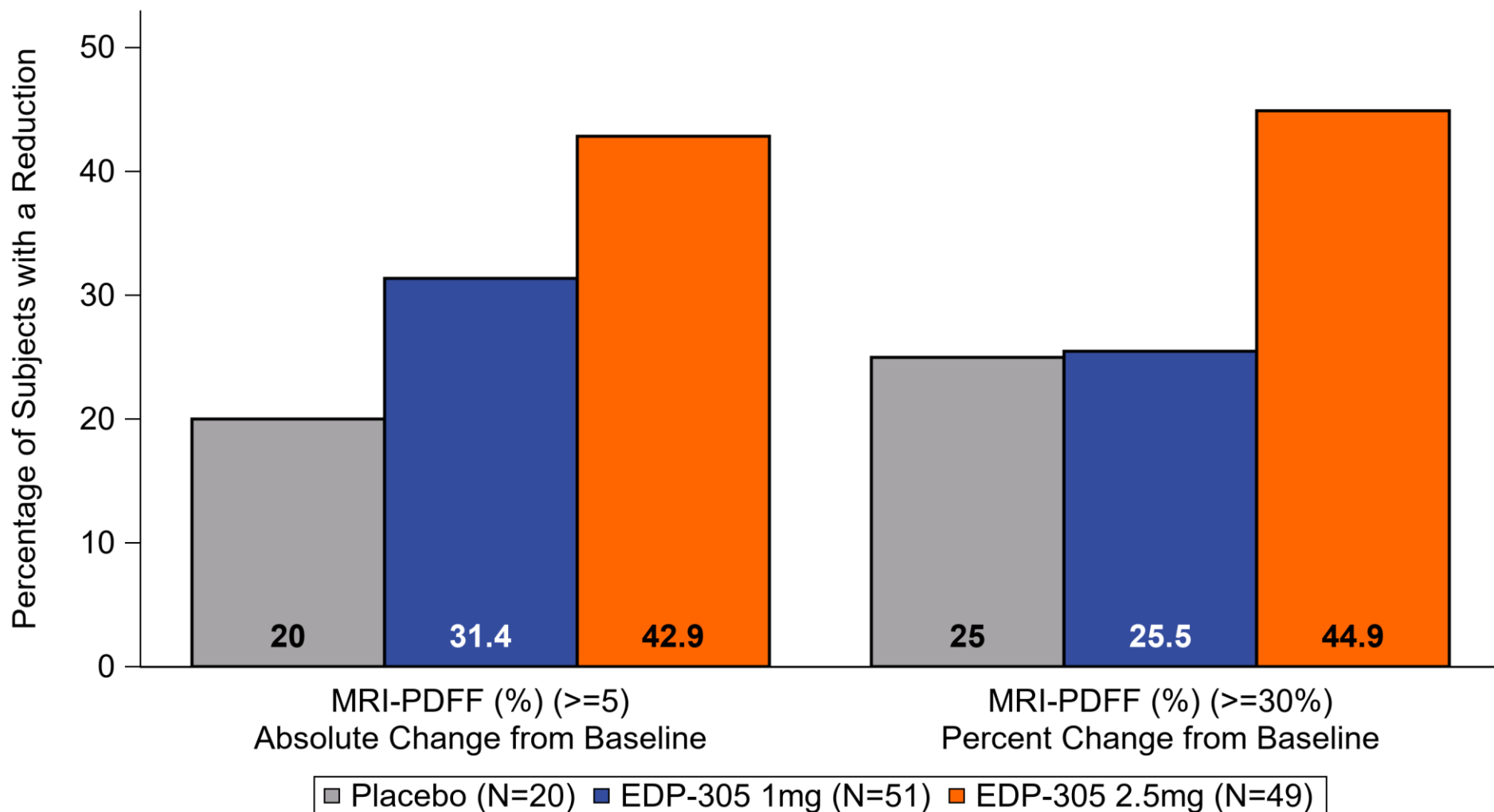
# MRI-PDFF Percent Change From Baseline at Week 12

## Efficacy Population

### Key Secondary Endpoint Was Met in the 2.5mg Arm

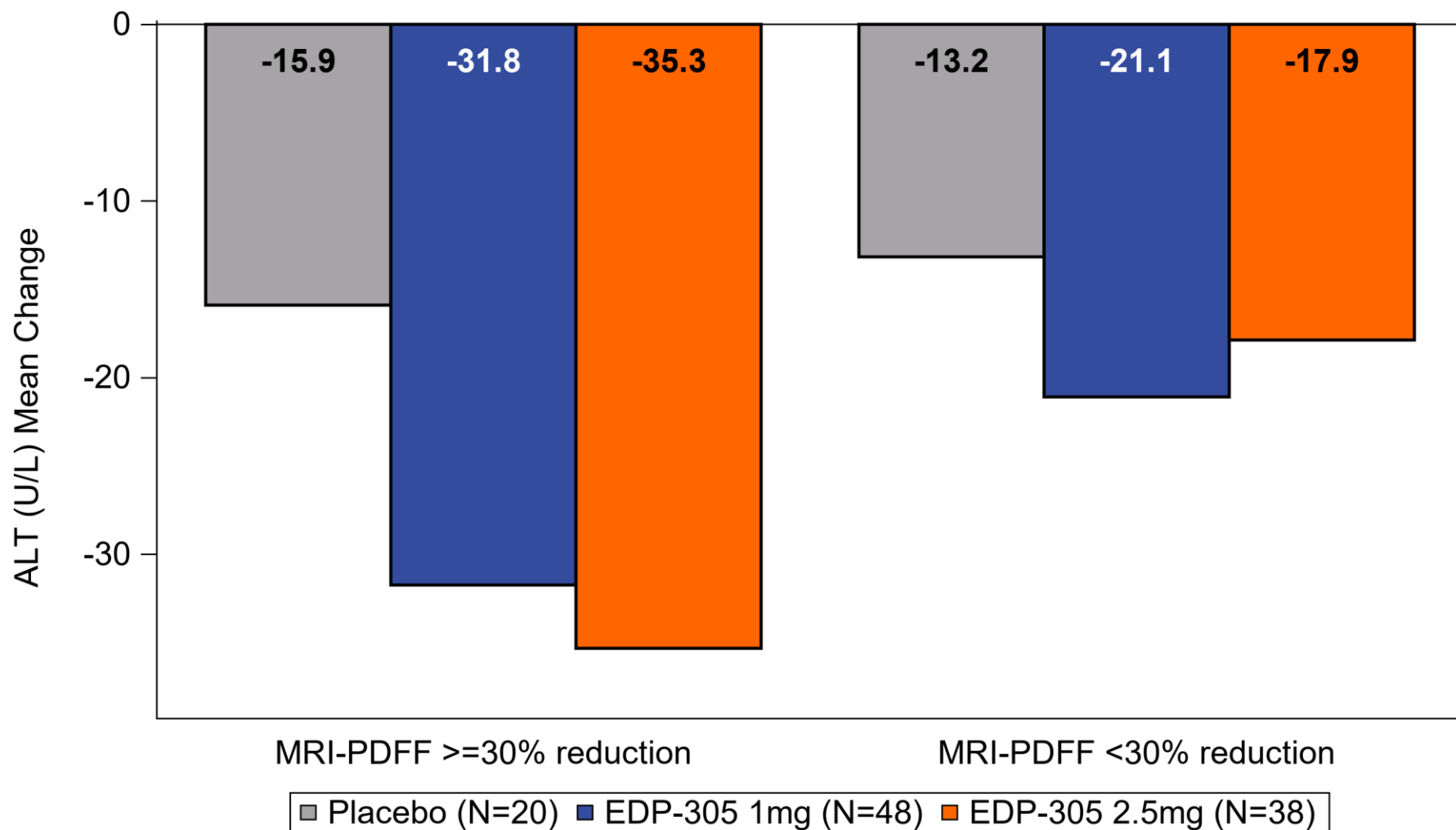


# Proportion of Subjects with Relative Change From Baseline (Absolute and Percent) in Liver Fat Reduction (%) at Week 12 Efficacy Population

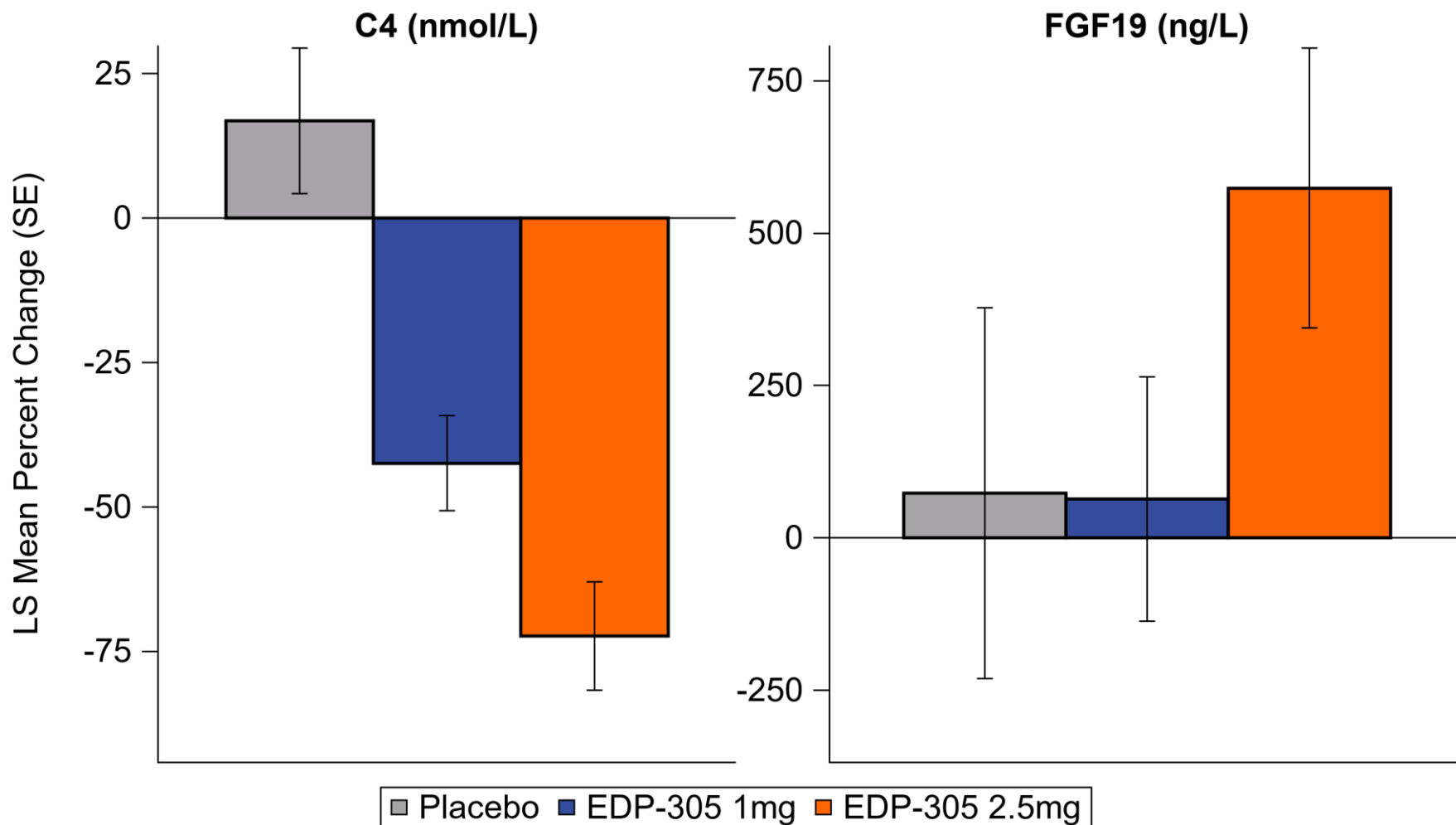


# Mean Change in ALT by MRI-PDFF Response at Week 12

## Efficacy Population

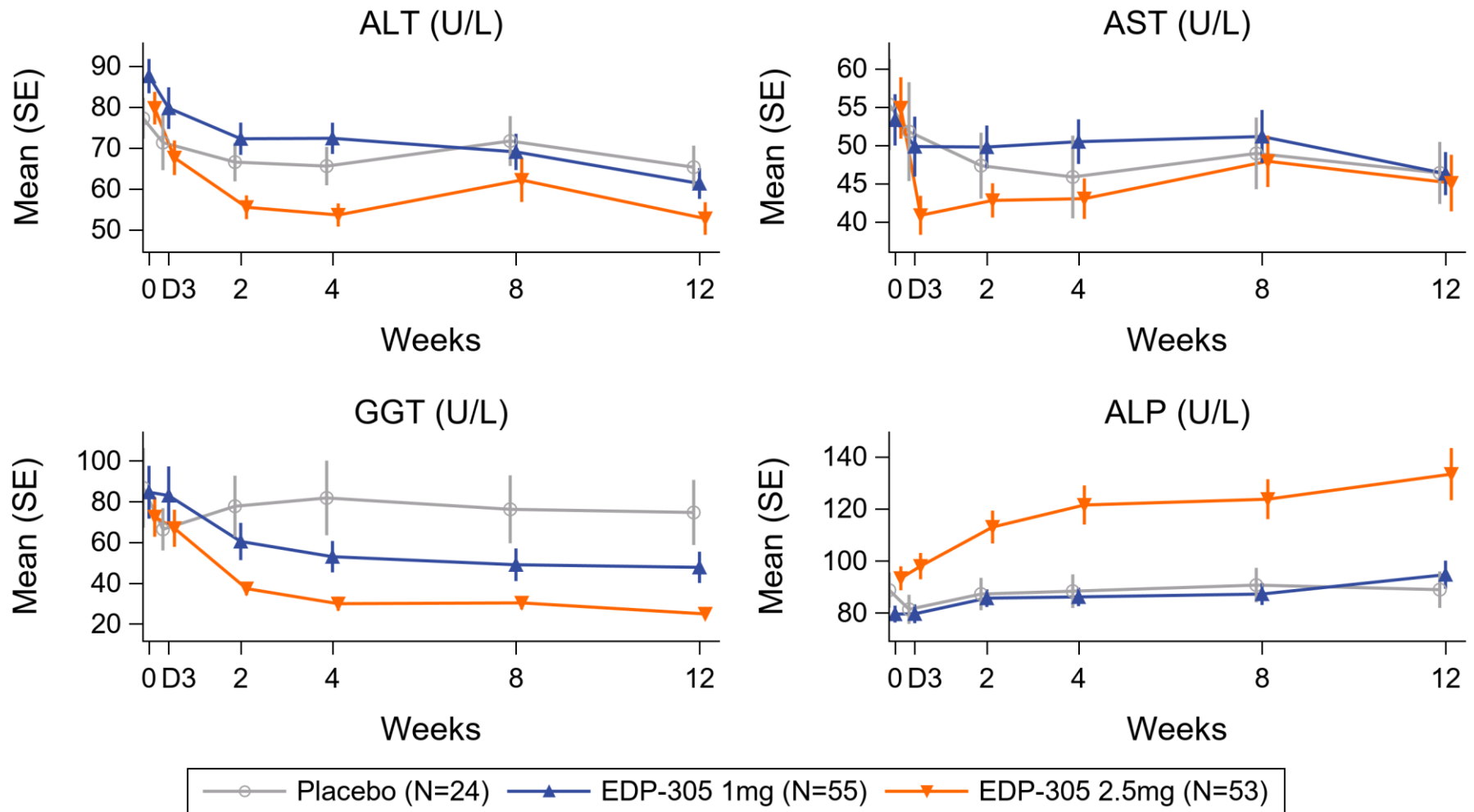


# Percentage Change in C4 and FGF19 (Pre-dose) at Week 12 - Efficacy Population



SE: standard error

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



SE: standard error

# Summary of Treatment-Emergent Adverse Events Safety Population

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

- 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 $\geq 5\%$ 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 <sup>a</sup> ( 7.5%)
Pruritus <sup>c</sup>	1 ( 4.2%)	0	3 <sup>b</sup> ( 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
- TEAEs are consistent with the observed safety profile of EDP-305 in >400 subjects exposed to the drug to date

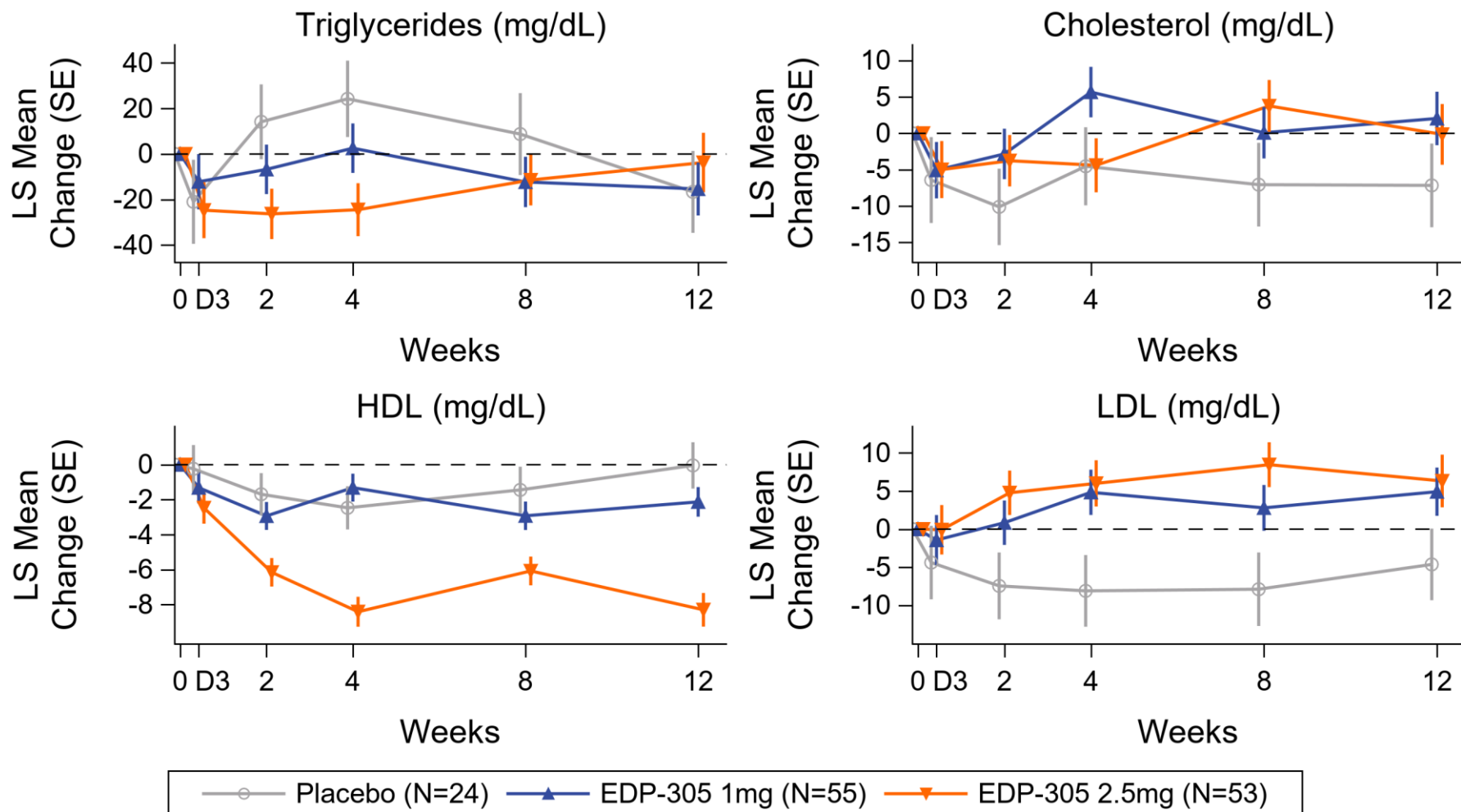
<sup>a</sup> Three of the 4 subjects are also counted in pruritus generalized

<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



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 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.  $\geq 30\%$  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 ( $\geq 5\%$ ) 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 on-going

# Acknowledgments

- 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

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# **ENANTA**

## **Pharmaceuticals**

**ARGON-1**