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Efruxifermin (EFX) in nonalcoholic steatohepatitis with fibrosis: results from a randomized, double-blind, placebo-controlled, phase 2b trial (HARMONY)

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Disclosures

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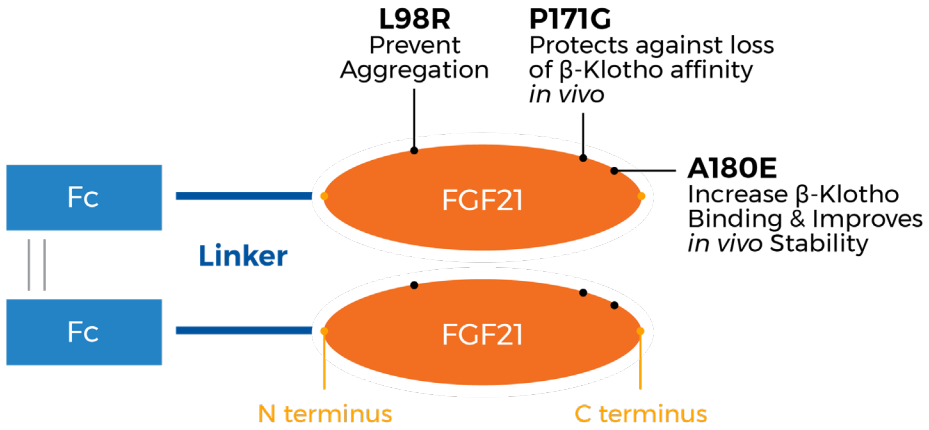
Introduction

EFX, A Long-Acting FGF21 Analog: FC Fusion Scaffold and 3 Point Mutations Extend Half-Life



Key Statistically Significant Findings from the Phase 2a BALANCED Study

- ↓ Liver fat
- ↓ ALT/AST
- ↓ Triglycerides
- ↓ Pro-C3/ELF
- ↓ HbA1c
- ↓ Body Weight

Encouraging Trend Toward
Fibrosis Improvement & NASH Resolution

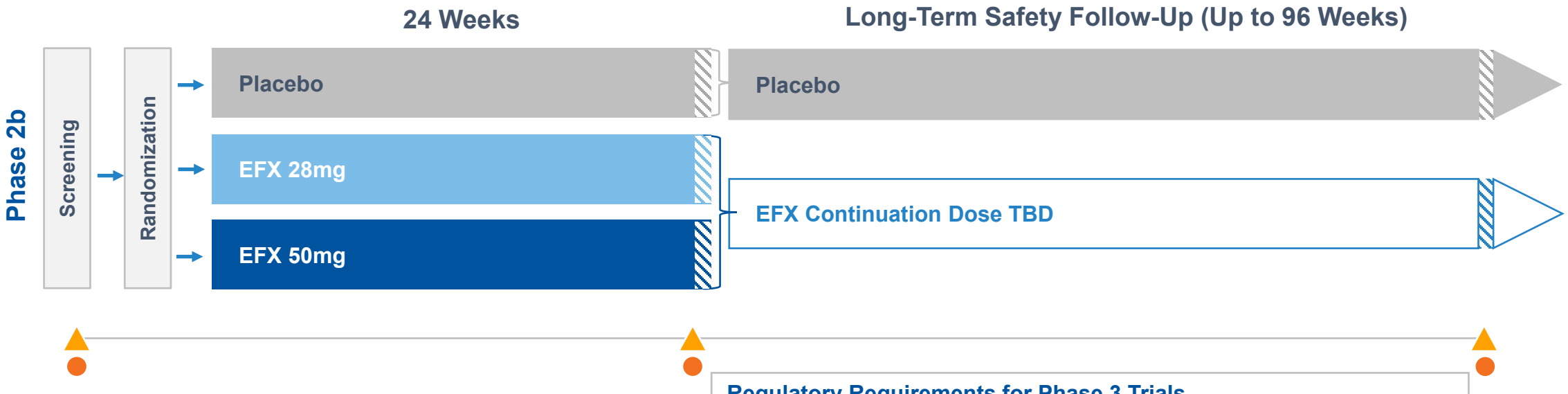
Stanislaus, S *et al.* (2017) *Endocrinology* 158(5): 1314-27; Lee, S *et al.* (2018) *Nature* 553: 501-505; Kharitonenkov, A *et al.* (2007) Endocrinology 148(2)774-781

HARMONY Trial Design and Objectives

Key Inclusion Criteria
- F2-F3 NASH
- NAS ≥4
- Liver Fat (MRI-PDFF) ≥8%

Phase 2b Primary Endpoint
- ≥ 1-stage fibrosis improvement without worsening of NASH

Key Secondary Efficacy Endpoints
- NASH Resolution & No Worsening of Fibrosis
- Fibrosis Markers
- Lipoproteins
- Glycemic Control
- Weight Change
- MRI-PDFF
- Liver Injury Markers

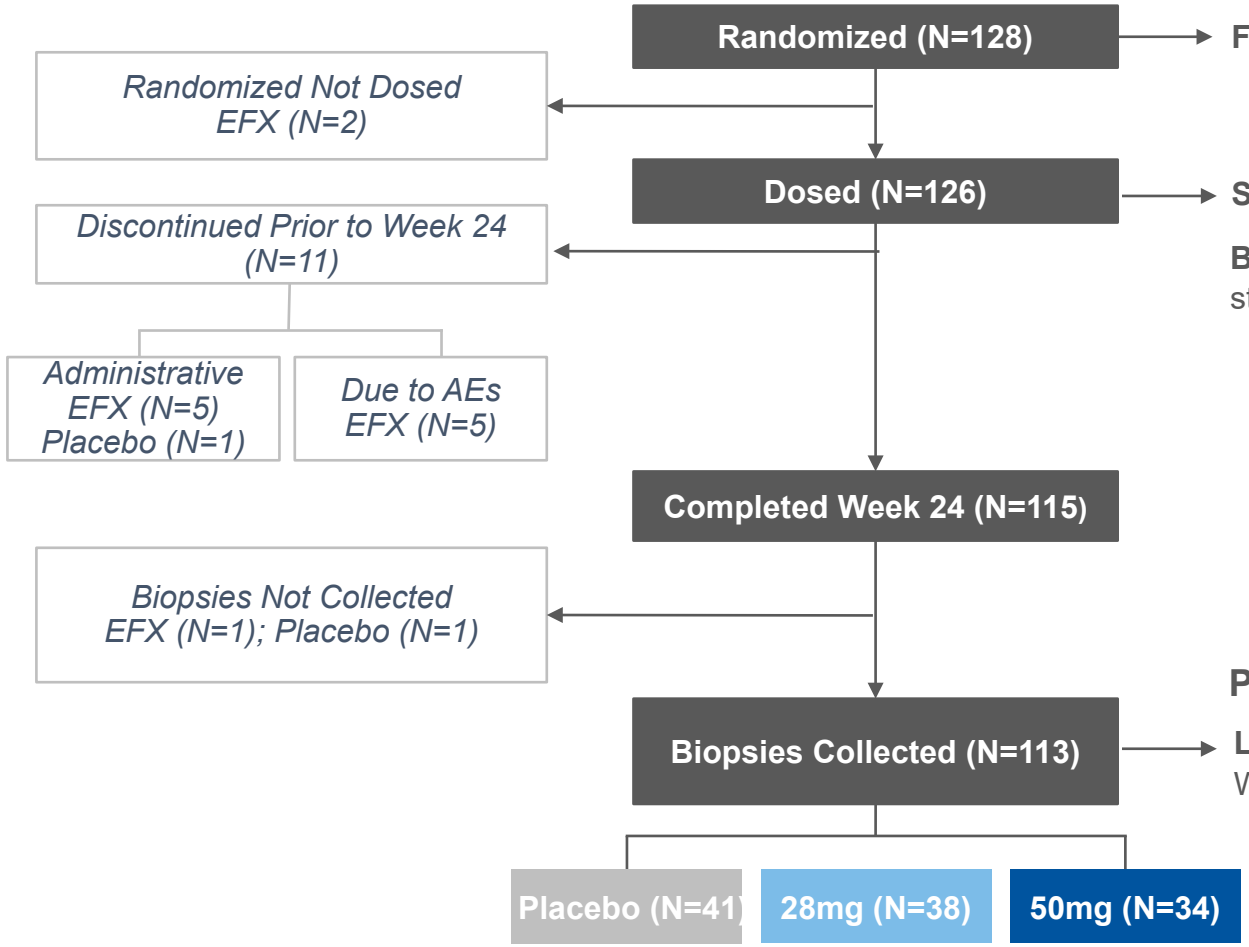


Regulatory Requirements for Phase 3 Trials
- FDA accepts one of two endpoints for Phase 3 registrational trials: (1) Fibrosis improvement ≥1 stage & no worsening of NASH or (2) NASH resolution and no worsening of fibrosis[1]
- EMA requires both endpoints to be met for marketing approval[2]

[1] FDA Draft Guidance, Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment (2018)

[2] EMA, Draft Reflection paper on regulatory requirements for the development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH) (2018)

HARMONY: Patient Disposition at Week 24



Key Analysis Sets

Full Analysis Set – All subjects who were randomized

Safety Set – All subjects who received at least one dose of study drug

Biomarker Analysis Set – All subjects who have baseline and on-study biomarker measurement at given timepoint

Primary Endpoint

Liver Biopsy Analysis Set – All subjects who have Baseline and Week 24 liver biopsy results

Baseline Demographics

Parameter (Mean)	Placebo (N=43)	EFX 28mg (N=42)	EFX 50mg (N=43)
Age (Years)	55	57	52
Sex (% Female)	63	69	53
Weight (kg)	108	104	103
Ethnicity (% Hispanic or Latino)	35	40	47
BMI (kg/m^2)	38.7	38.3	37.2
Type 2 Diabetes (%)	65	76	70
Fibrosis Stage (% F3)[1]	70	64	63
Enhanced Liver Fibrosis (ELF) Score	9.8	9.7	9.8
Pro-C3[2] (µg/L)	16.5	15.3	18.4
Liver Stiffness by VCTE[3] (FibroScan) (kPa)	15	14	16
Hepatic Fat Fraction by MRI-PDFF[4] (%)	17.1	18.5	17.5
NAFLD Activity Score (NAS)	5.4	5.1	5.6
Alanine Aminotransferase (ALT) (U/L)	62	50	63
Aspartate Aminotransferase (AST) (U/L)	57	42	52
HbA1c (%)	6.8	6.8	6.7
in Type 2 Diabetes subgroup	7.2	7.2	7.1
Triglycerides (mg/dL)	170	158	154
LDL-Cholesterol (mg/dL)	94	96	111

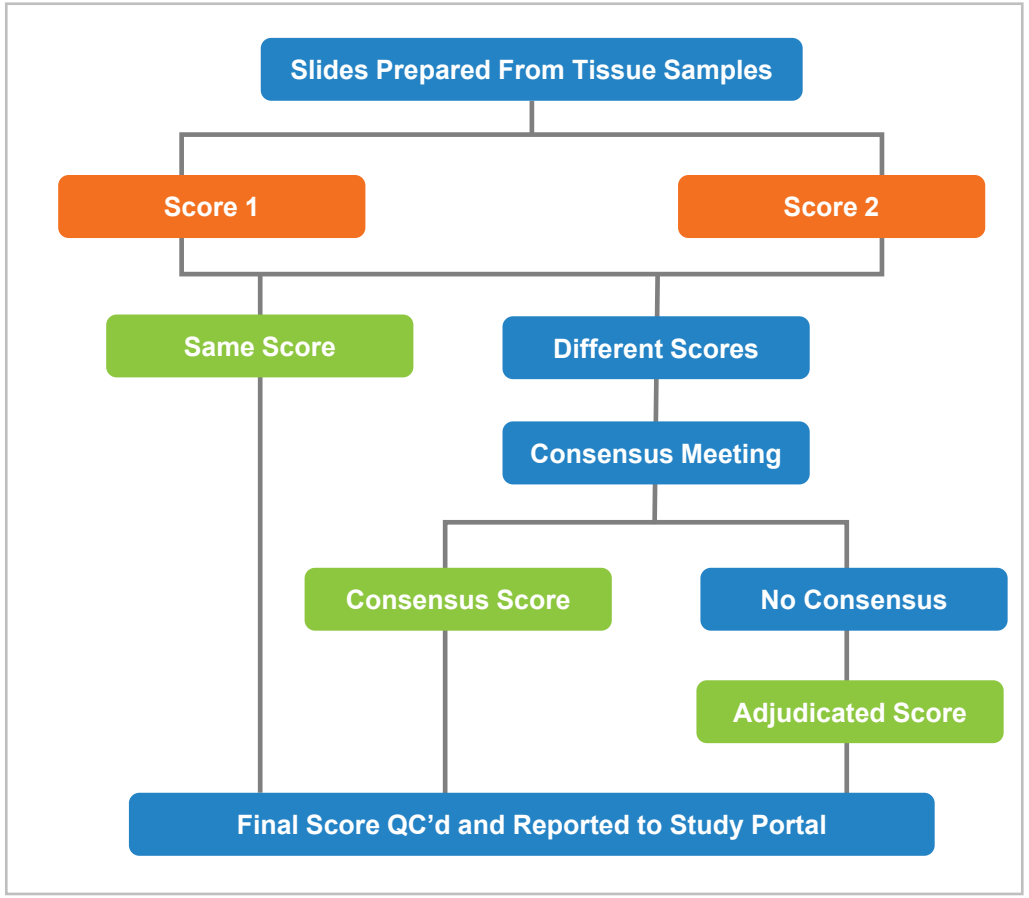
[1] All patients either fibrosis stage 2 (F2) or stage 3 (F3); [2] Procollagen 3 N-Terminal Propeptide; [3] Vibration-controlled transient elastography; [4] Magnetic Resonance Imaging Proton Density Fat Fraction

Consensus Reading of Biopsies: Rigorous Approach to Histopathology Based on FDA Input to Minimize Variability

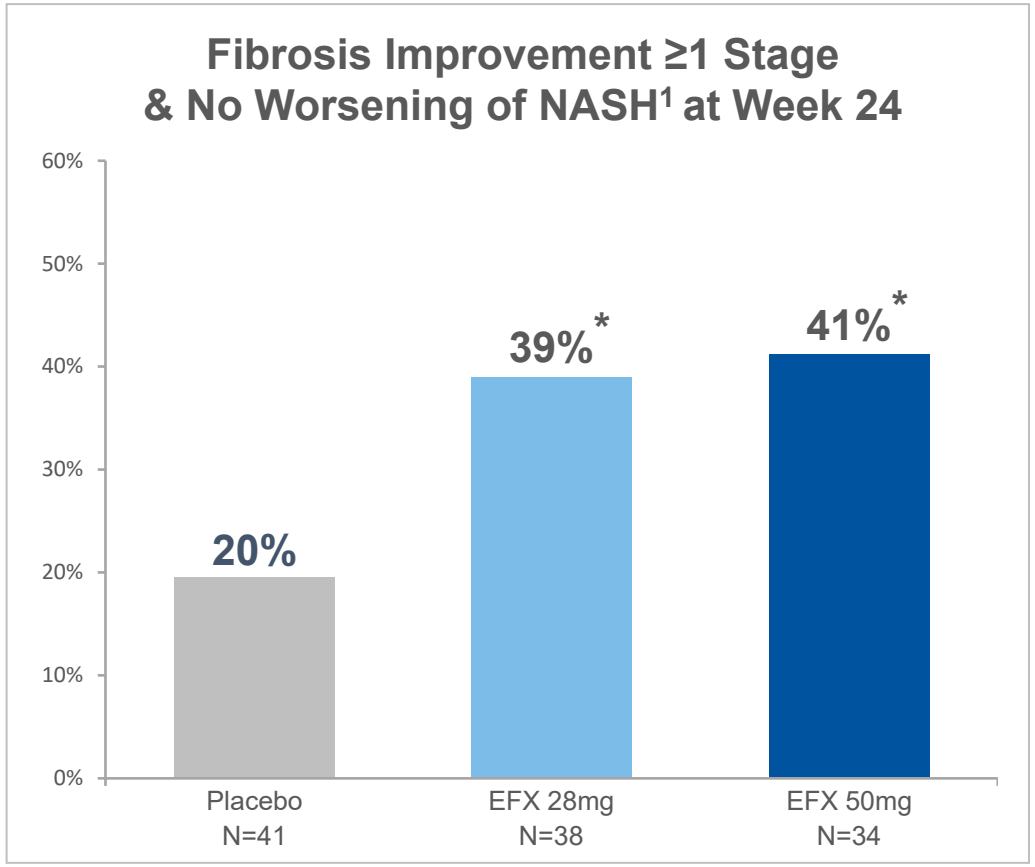
Key Features of EFX Biopsy Analysis Plan

- Biopsies independently scored by two pathologists, with a third pathologist available to adjudicate in absence of consensus
- Pathologists underwent protocol-specific training to align on NASH-CRN scoring interpretation
- Pathologists blinded to subject, treatment, and sequence
- No paired biopsy reads (i.e., pre- and on-treatment biopsies not read side-by-side)

Consensus Biopsy Analysis Flow Chart

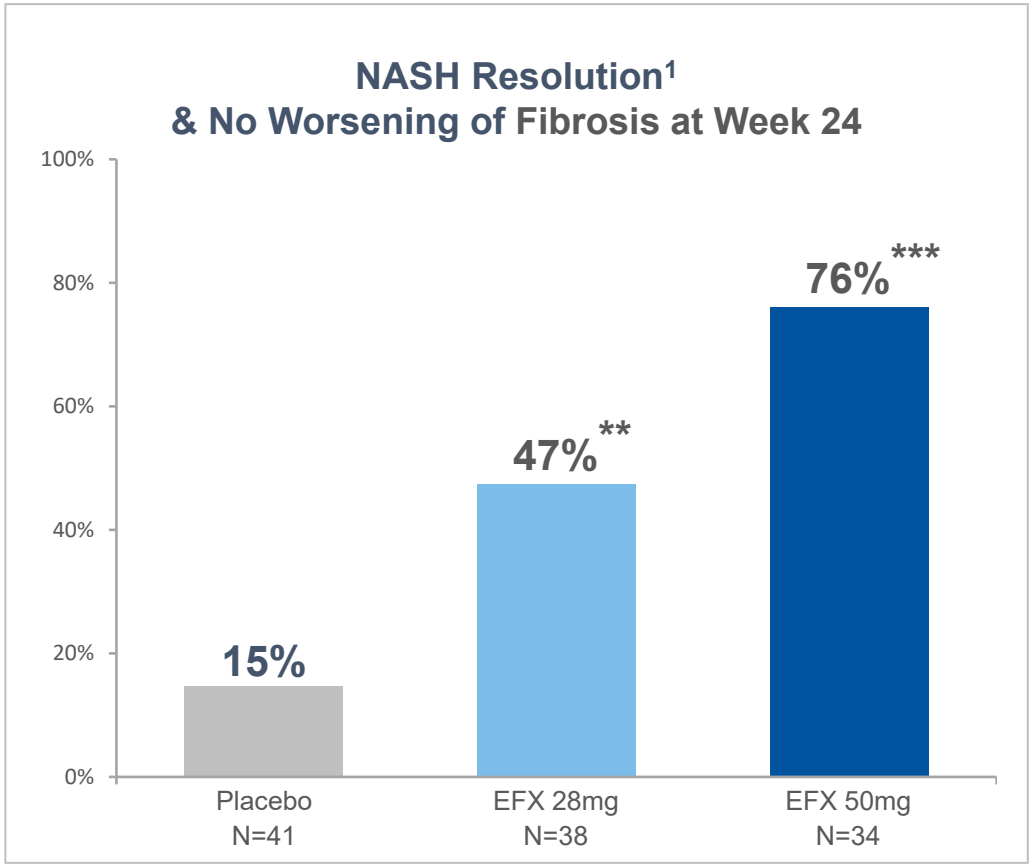


Both EFX Doses Achieved Statistical Significance on Fibrosis Improvement and NASH Resolution



[1] Improvement in liver fibrosis greater than or equal to one stage and no worsening of NASH (defined as no increase in NAS for ballooning, inflammation, or steatosis)

* p<0.05, versus placebo (Cochran–Mantel–Haenszel test [CMH])

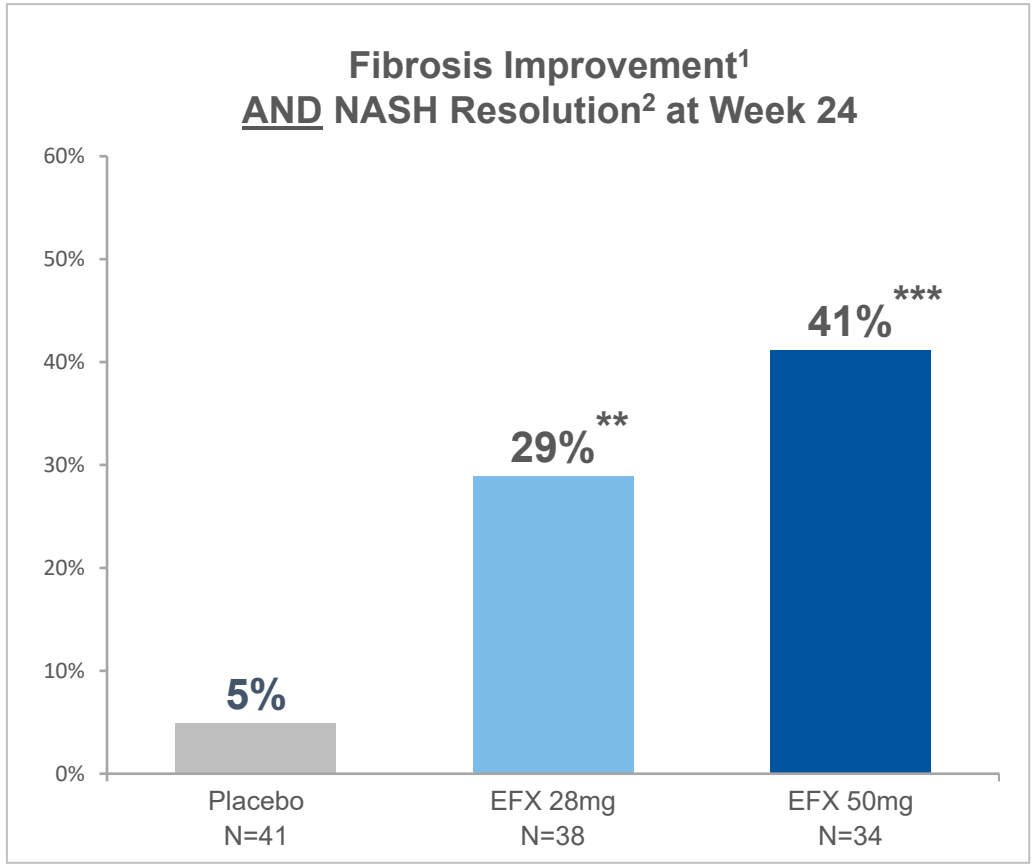


[1] NAS score of 0 or 1 for lobular inflammation and a score of 0 for ballooning

** p<0.01, *** p<0.001, versus placebo (CMH)

Source Data: Liver Biopsy Analysis Set

Both EFX Doses Also Achieved Statistical Significance on Composite Endpoint (Fibrosis Improvement and NASH Resolution)



[1] Improvement in liver fibrosis greater than or equal to one stage
[2] NAS score of 0 or 1 for lobular inflammation and a score of 0 for ballooning
** p<0.01, *** p<0.001, versus placebo (CMH)

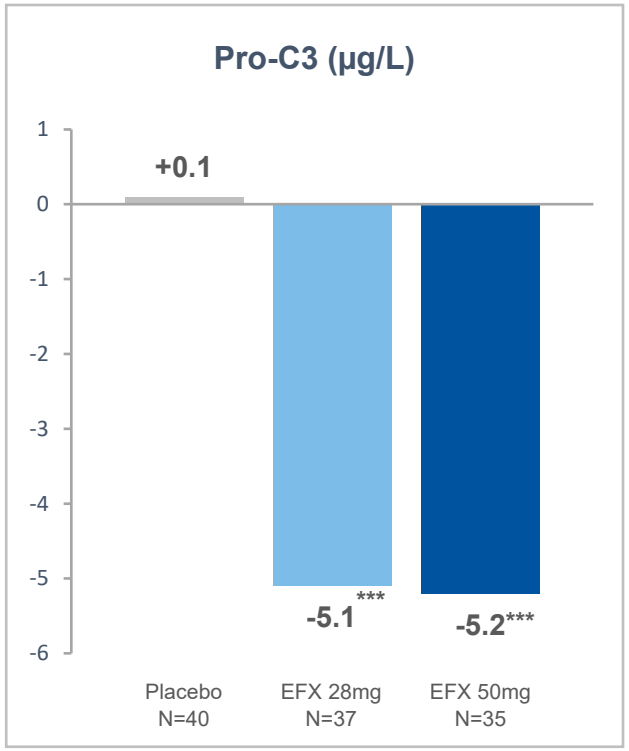
Patients Achieving Fibrosis Improvement ≥2 Stages and No Worsening of NASH at Week 24

Placebo (N=41)	EFX 28mg (N=38)	EFX 50mg (N=34)
5%	16%	15%

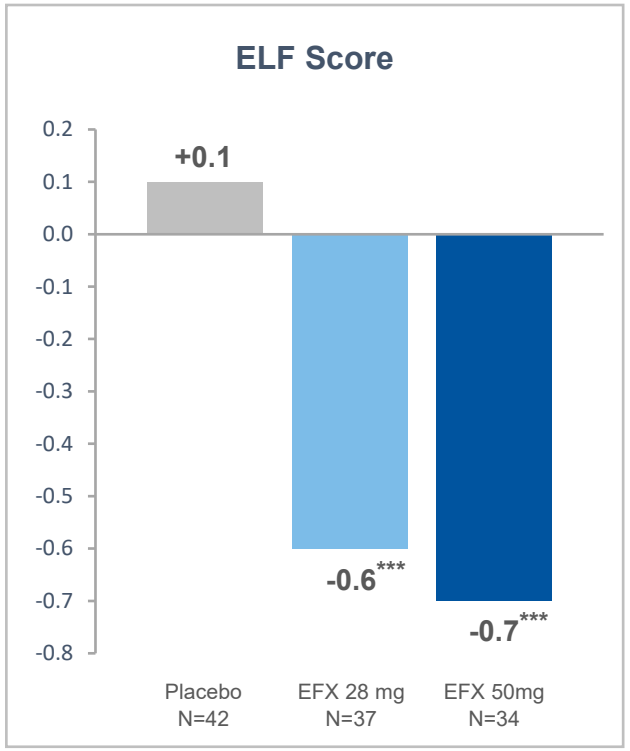
Source Data: Liver Biopsy Analysis Set

Statistically Significant Reductions in Non-Invasive Markers Reflect Histological Improvement in Fibrosis

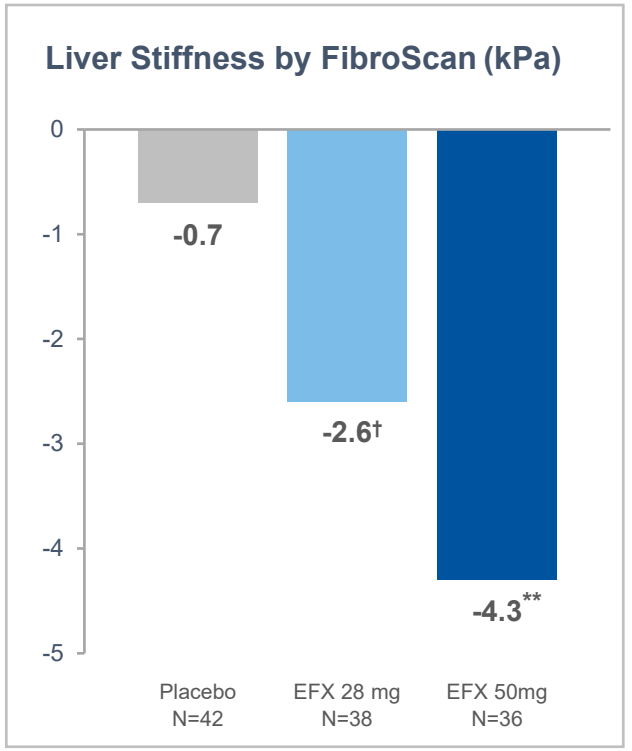
LS Mean Change From Baseline to Week 24



*** p<0.001, versus placebo (MMRM[1])



*** p<0.001, versus placebo (MMRM[1])

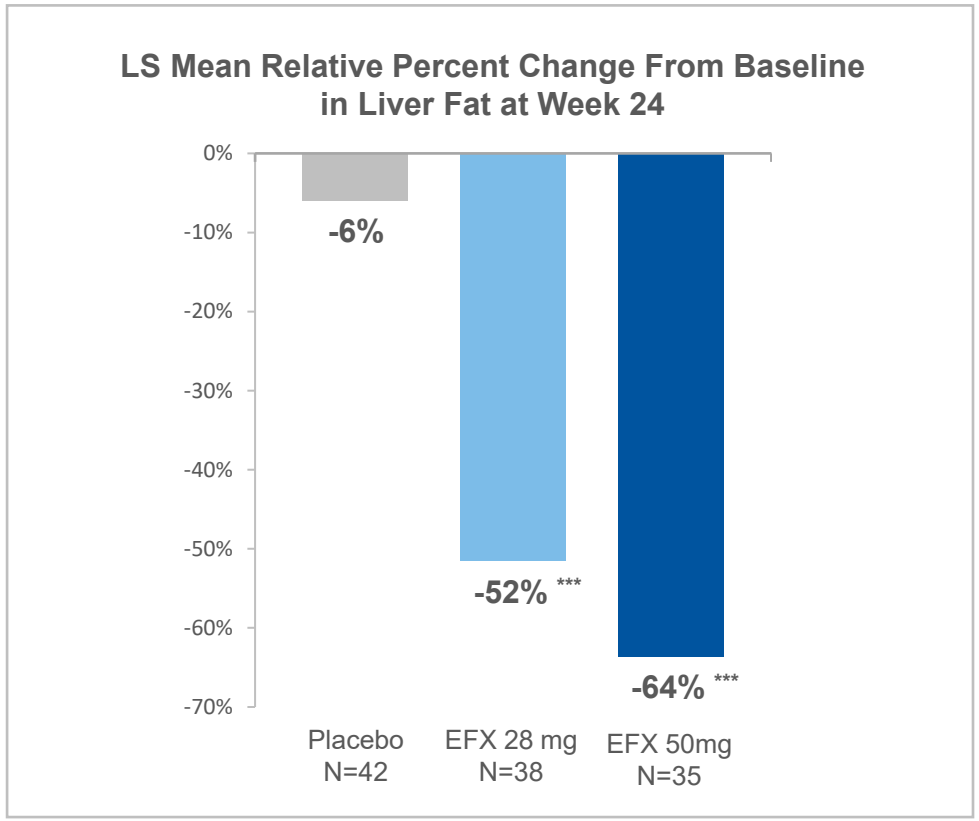


** p<0.01, versus placebo (ANCOVA[2])
† p<0.01, versus baseline (ANCOVA)

[1]Mixed-model repeated-measures
[2]Analysis of Covariance

Source Data: Biomarker Analysis Set (Pro-C3 and ELF); Full Analysis Set (Liver Stiffness) (non-missing values only, no imputation)

EFX Substantially Reduced and Normalized Liver Fat, Showing Potential to Eliminate the Underlying Disease Driver



*** p<0.001, versus placebo (ANCOVA)

Proportion of Patients Achieving Fat Reduction Thresholds at Week 24

Endpoint	Placebo (N=42)	EFX 28mg (N=38)	EFX 50mg (N=35)
Relative Reduction in Liver Fat			
≥50%	2%	63% ***	77% ***
Normalization of Liver Fat Content (from >5% to <5%)			
≤5%	0%	34% ***	51% ***

*** p<0.001, versus placebo (CMH)

Source Data: MRI-PDFF Analysis Set (All subjects who have Baseline and Week 24 liver fat measurements)

Rapid and Sustained Statistically Significant Improvements in Markers of Liver Injury

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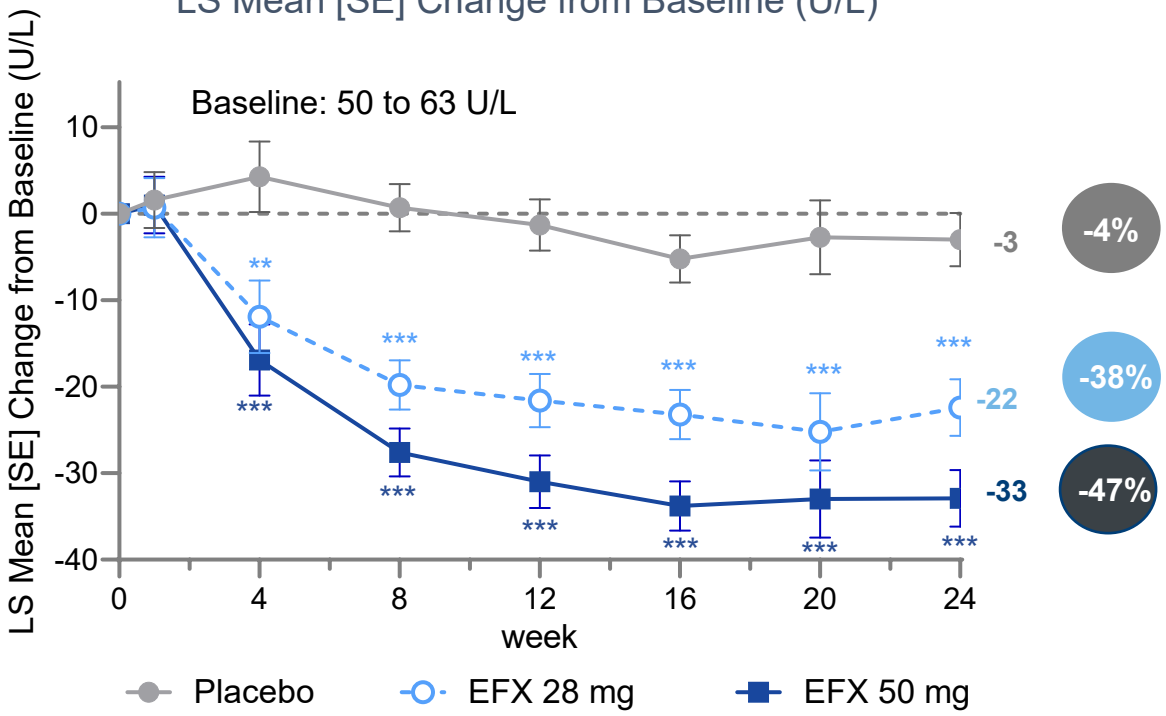
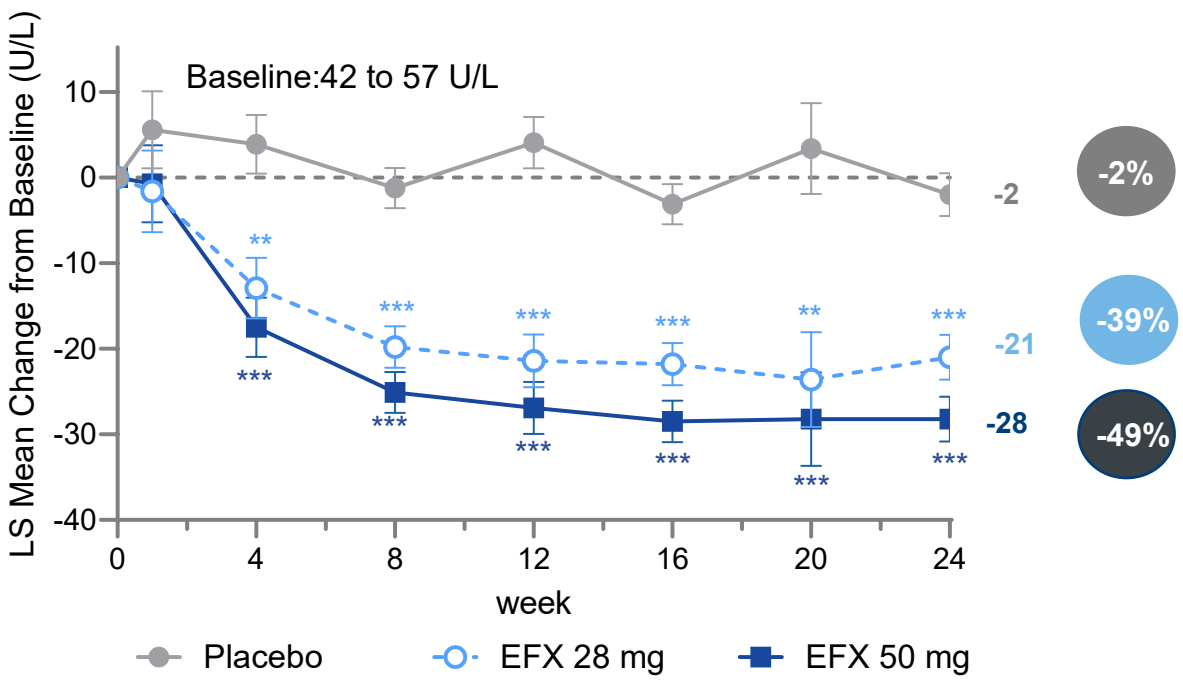
Alanine Aminotransferase (ALT)
LS Mean [SE] Change from Baseline (U/L)



Aspartate Aminotransferase (AST)
LS Mean [SE] Change from Baseline (U/L)



Statistically significant improvements also observed for GGT & ALP

* p<0.05, ** p<0.01, *** p<0.001, versus placebo (MMRM)
† p<0.05, †† p<0.01, versus baseline (MMRM)

[1]Source Data: Full Analysis Set

Treatment-Emergent Adverse Events (TEAE)

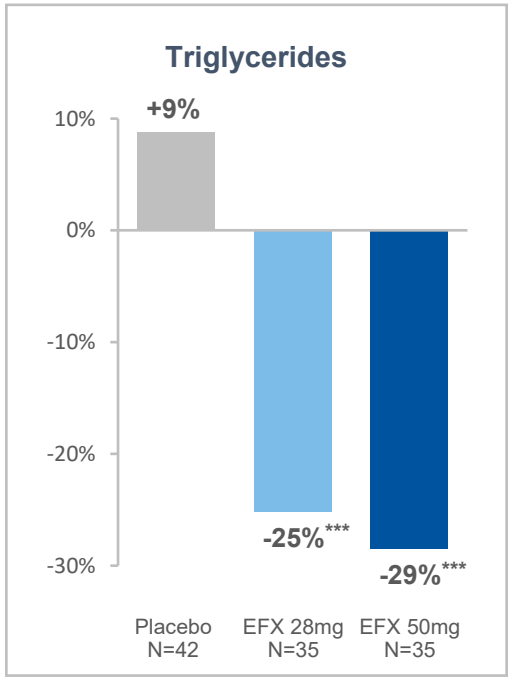
TEAE Overview	Placebo (N=43)	EFX 28mg (N=40)	EFX 50mg (N=43)
TEAE Leading to Death	0 (0%)	0 (0%)	0 (0%)
Drug-Related Serious Adverse Event (SAE)	0 (0%)	0 (0%)	1 (2%)[a,b]
Drug-Related TEAE Leading to Discontinuation	0 (0%)	2 (5%)[c]	2 (5%)[d,e]
Most Frequent (≥15%) Drug-Related TEAEs	**Placebo**	**EFX 28mg**	**EFX 50mg**
Diarrhea	6 (14%)	14 (35%)	14 (33%)
Nausea	5 (12%)	10 (25%)	14 (33%)
Increased Appetite	2 (5%)	7 (18%)	10 (23%)
Frequent Bowel Movements	1 (2%)	8 (20%)	0 (0%)
Injection Site Erythema	5 (12%)	6 (15%)	7 (16%)
Injection Site Bruising	1 (2%)	6 (15%)	3 (7%)

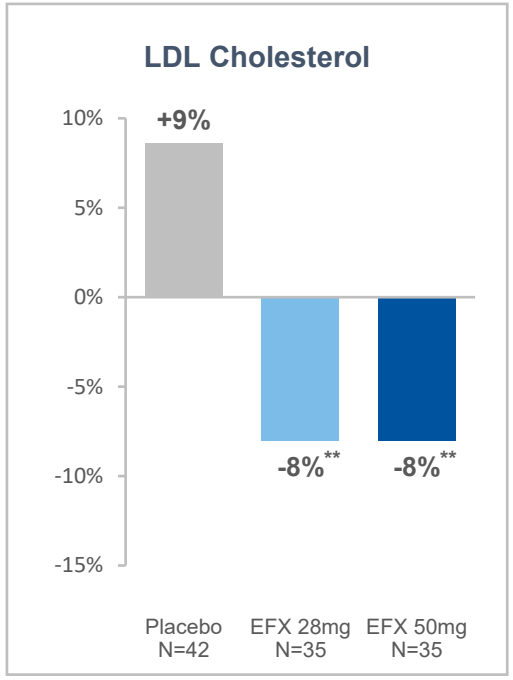
[a] (1) Esophagitis
[b] There were three additional non-drug-related SAEs: (1) Edema; (2) Covid-19; (3) Pancreatitis
[c] (1) Increased appetite & weight gain; (2) diarrhea
[d] (1) Esophagitis & vomiting; (2) Nausea
[e] There was one additional non-drug-related AE: Lymphadenopathy

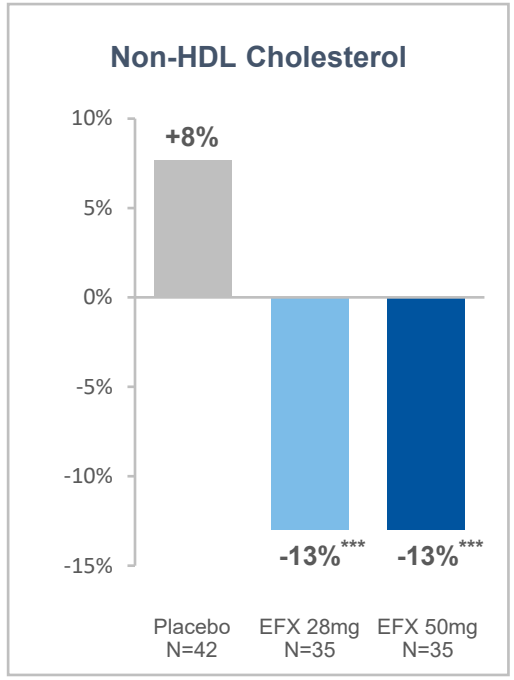
Source Data: Safety Set

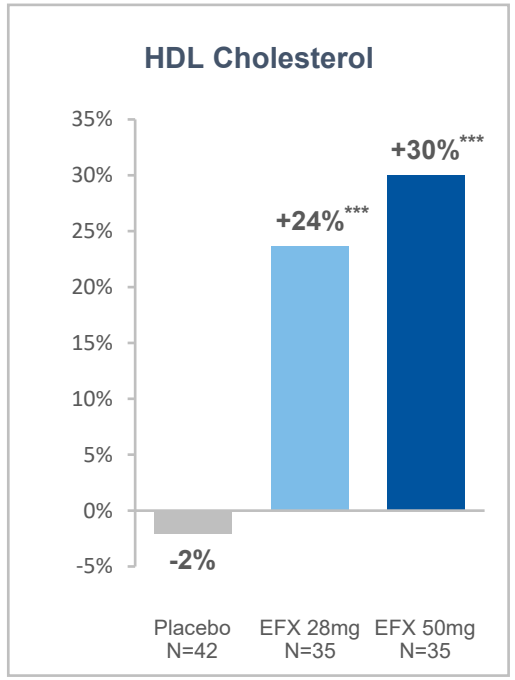
Significant Improvements Observed in Lipoprotein Profile

LS Mean Change From Baseline to Week 24 (%)









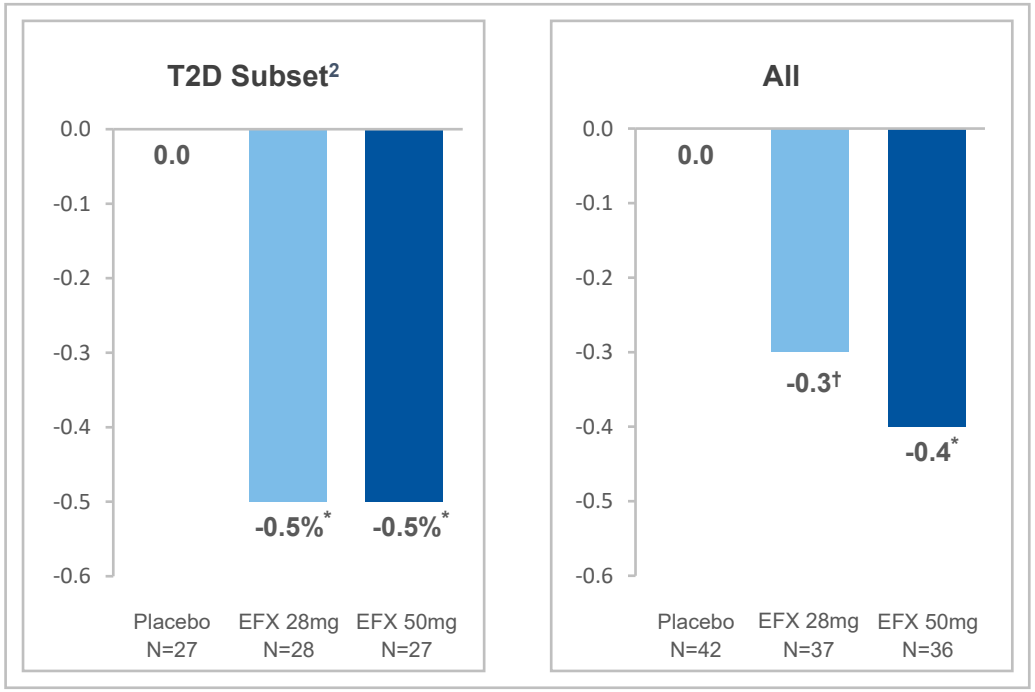
** p<0.01, *** p<0.001 versus placebo (MMRM)

Source Data: Full Analysis Set, non-missing values only, no imputation

Clinically Meaningful Improvements Observed in Glycemic Control and Insulin Sensitivity

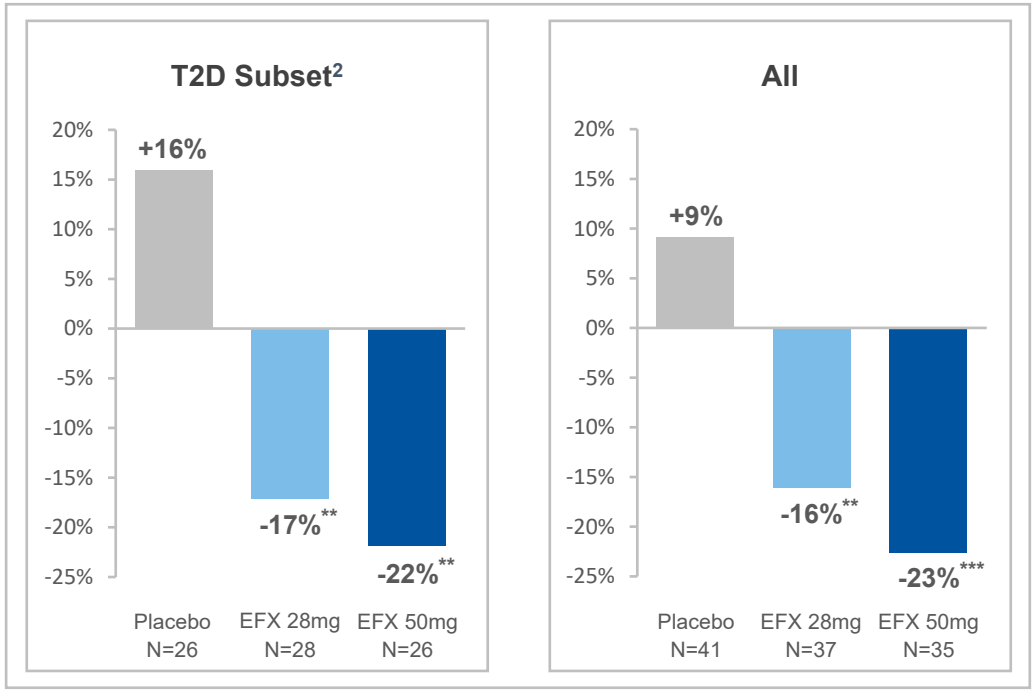
LS Mean Change From Baseline to Week 24

HbA1c(%)[1]



* p<0.05, versus placebo (MMRM); † p<0.05, versus baseline (MMRM)

C-Peptide[3]

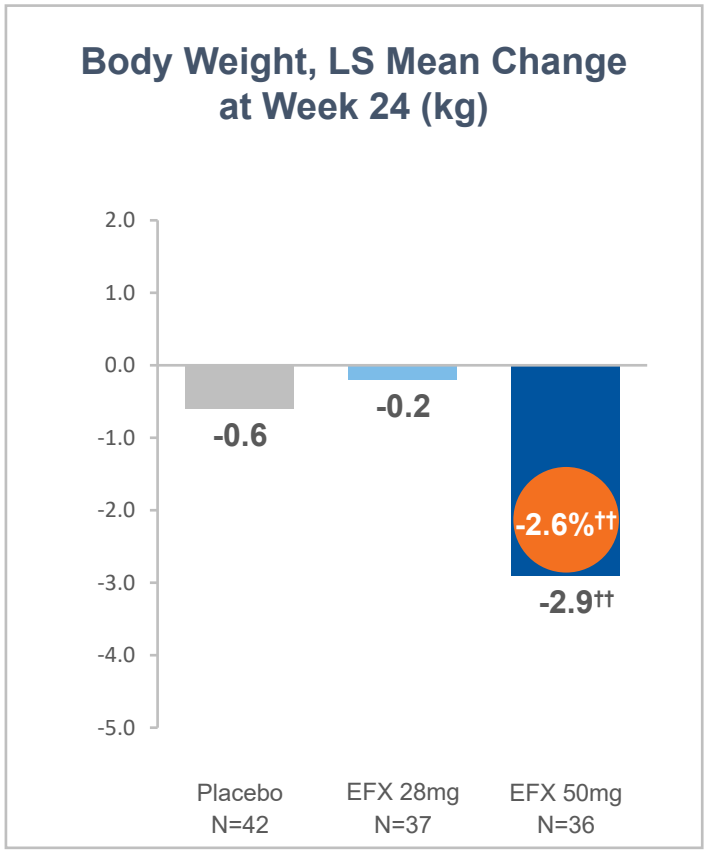


** p<0.01, *** p<0.001, versus placebo (MMRM)

[1] Absolute change from baseline, %; [2] Patients remained on diabetic medications; [3] Relative percent change from baseline

Source Data: Biomarker Analysis Set

Weight Loss Observed for 50mg EFX Dose Group



†† p<0.01, versus baseline (MMRM)

Source Data: Full Analysis Set, non-missing values only, no imputation

Summary and Future Directions

Both EFX doses achieved a statistically significant difference from placebo for ≥ 1-stage fibrosis improvement and NASH resolution

EFX also

- improved markers of liver injury and noninvasive markers of fibrosis
- improved lipoprotein profile and glycemic control
- led to weight loss on 50 mg
- was generally well tolerated with low numbers of treatment discontinuations

These data support initiation of EFX Phase 3 program

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