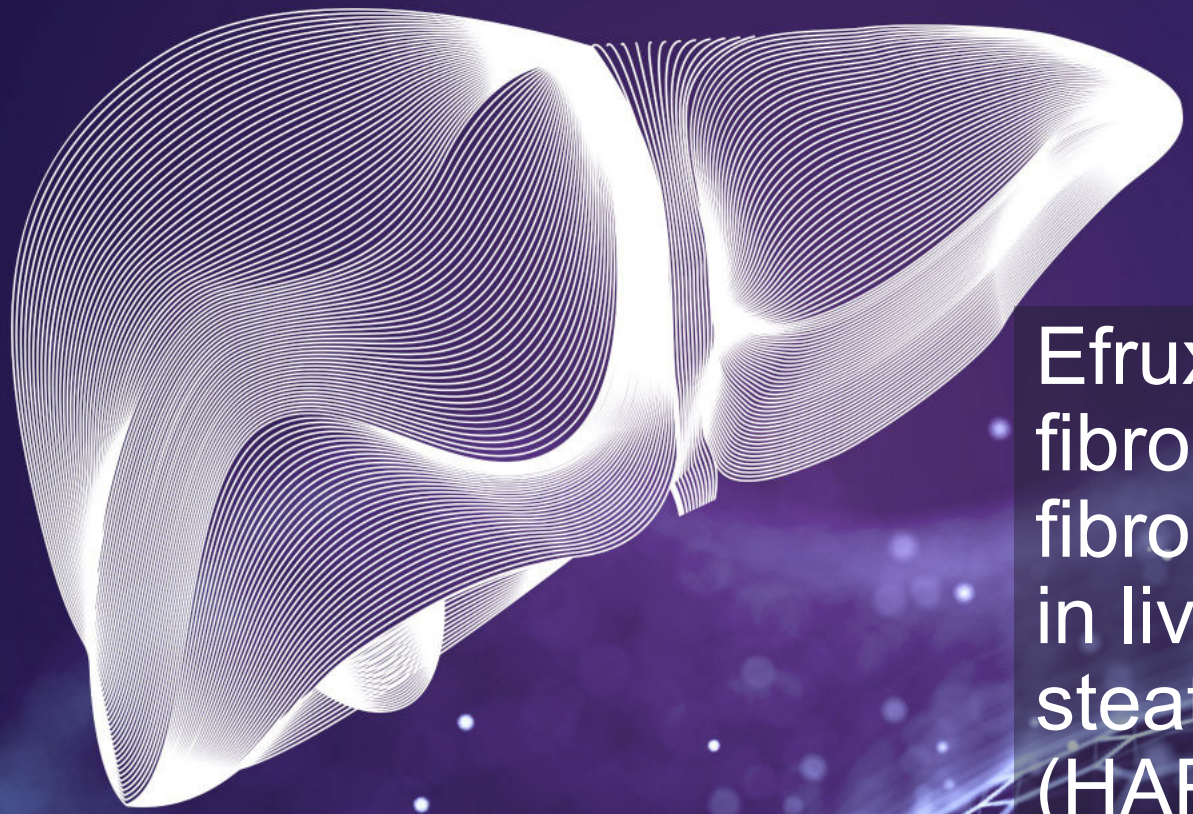


EASL CONGRESS 2024
Milan, Italy
5–8 June

Efruxifermin significantly reduced liver fibrosis in MASH patients with F2–F3 fibrosis, with sustained improvement in liver injury and resolution of steatohepatitis over 96 weeks (HARMONY phase 2b study)

June 8, 2024

Stephen A Harrison[1], Juan P Frias[2], Guy Neff[3], Gary A Abrams[4], K Jean Lucas[5], William Sanchez[6], Sudhanshu Gogia[7], Muhammed Y Sheikh[8], Cynthia Behling[9], Pierre Bedossa[10], Lan Shao[11], Doreen Chan[12], Erica Fong[12], Brittany de Temple[12], Matt Minerva[12], Kim Barrett[12], Reshma Shringarpure[12], Erik J Tillman[12], Timothy Rolph[12], Andrew Cheng[12], Vlad Ratziu[13], Kitty Yale[12]

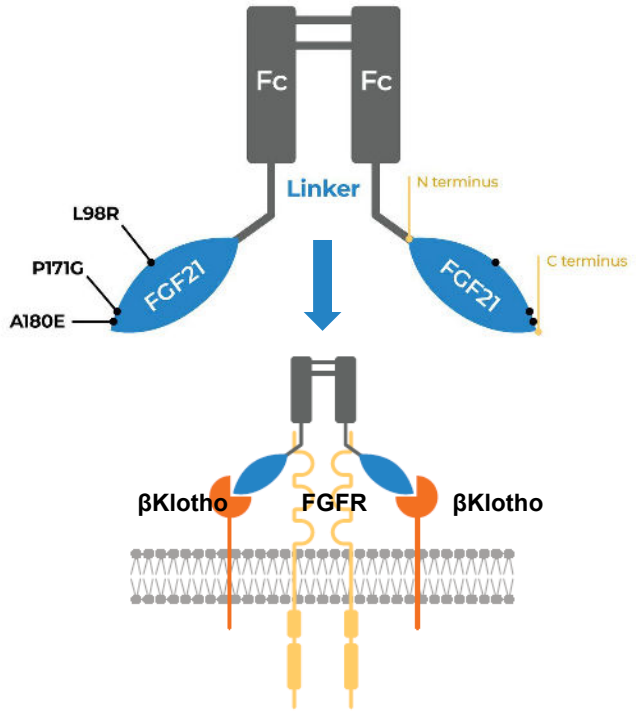
[1]Department of Hepatology, University of Oxford, Oxford, UK; [1]Pinnacle Clinical Research, San Antonio, TX, USA; [2]Velocity Clinical Research, Los Angeles, CA, USA; [3]Covenant Metabolic Specialists, Sarasota, FL, USA; [4]Department of Medicine, Prisma Health Upstate, Greenville, SC, USA; [5]Lucas Research, Morehead, NC, USA; [6]Floridian Clinical Research, Miami Lakes, FL, USA; [7]Texas Digestive Disease Institute, Webster, TX, USA; [8]Fresno Clinical Research Center, Fresno, CA, USA; [9]Department of Pathology, Sharp Memorial Hospital, San Diego, CA, USA; [10]Liverpat, Paris, France; [10]Institute of Cellular Medicine, University of Newcastle, Newcastle upon Tyne, UK; Statistics, [11]Fortrea Inc, [12]Akero Therapeutics, South San Francisco, CA, USA , [13] Sorbonne University, Paris France

Disclosures

- Consulting for Madrigal, Novo-Nordisk, Boehringer-Ingelheim, 89Bio, Sagimet
- Grants to institution: Merck

In recognition of Dr. Stephen A. Harrison and his role in EFX Development

Efruxifermin (EFX) is an engineered, bivalent Fc-FGF21 analog



Key attributes

- Akero proprietary Fc-FGF21, Point mutations
- Increases half-life from < **2 hours** to **~3 days**
- **High affinity** for β-Klotho
- Better translation to **human** pharmacology
- **Balanced potency** at FGFR1c, 2c, 3c
- **Inactive** at FGFR4

MASH Trials with EFX

Trial	Publication
Ph 2a (F1-F3)	**Nat Med 2021** 27(7):1262–71
Ph 2a (F4)	**JHEP Reports 2023** 5(1):100563
Ph 2b (F2-F3) Week 24 results	**Lancet Gastro Hepatol 2023** 2023;8(12):1080–1093
Ph 2b (F4) Week 36 results	**AASLD 2023** Late-breaking abstract 5005 *Hepatology* 2024; 79:E33 – E85.
Ph 2b (F1-F3; T2D) EFX+GLP-1RA	**Clin Gastroenterol Hepatol** 2024;S1542–3565(24): 00226–X

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

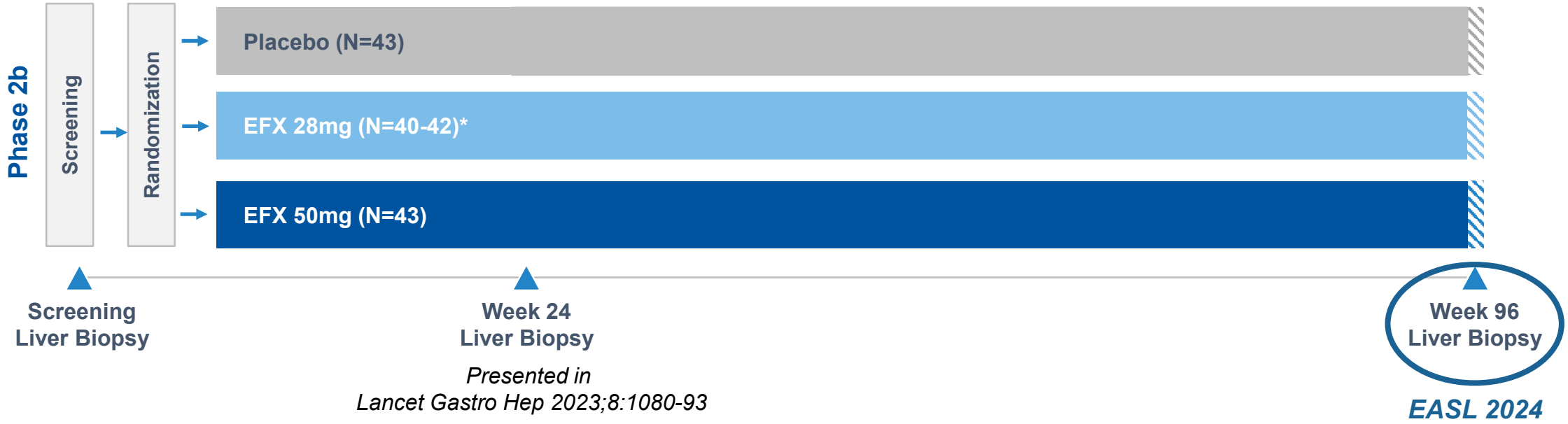
HARMONY Phase 2b Trial Design: Pre-Cirrhotic (F2-F3) MASH with Liver Histology at 24 and 96 weeks

Week 24 Primary Endpoint

- ≥ 1 stage fibrosis improvement & no worsening of MASH

Week 96 Endpoints

- ≥ 1 or 2 stages fibrosis improvement & no worsening of MASH
- MASH Resolution & No Worsening of Fibrosis
- Fibrosis Improvement & MASH Resolution



Presented in
Lancet Gastro Hep 2023;8:1080-93

EASL 2024

*N=42 randomized; N=40 randomized and dosed

Baseline Demographics

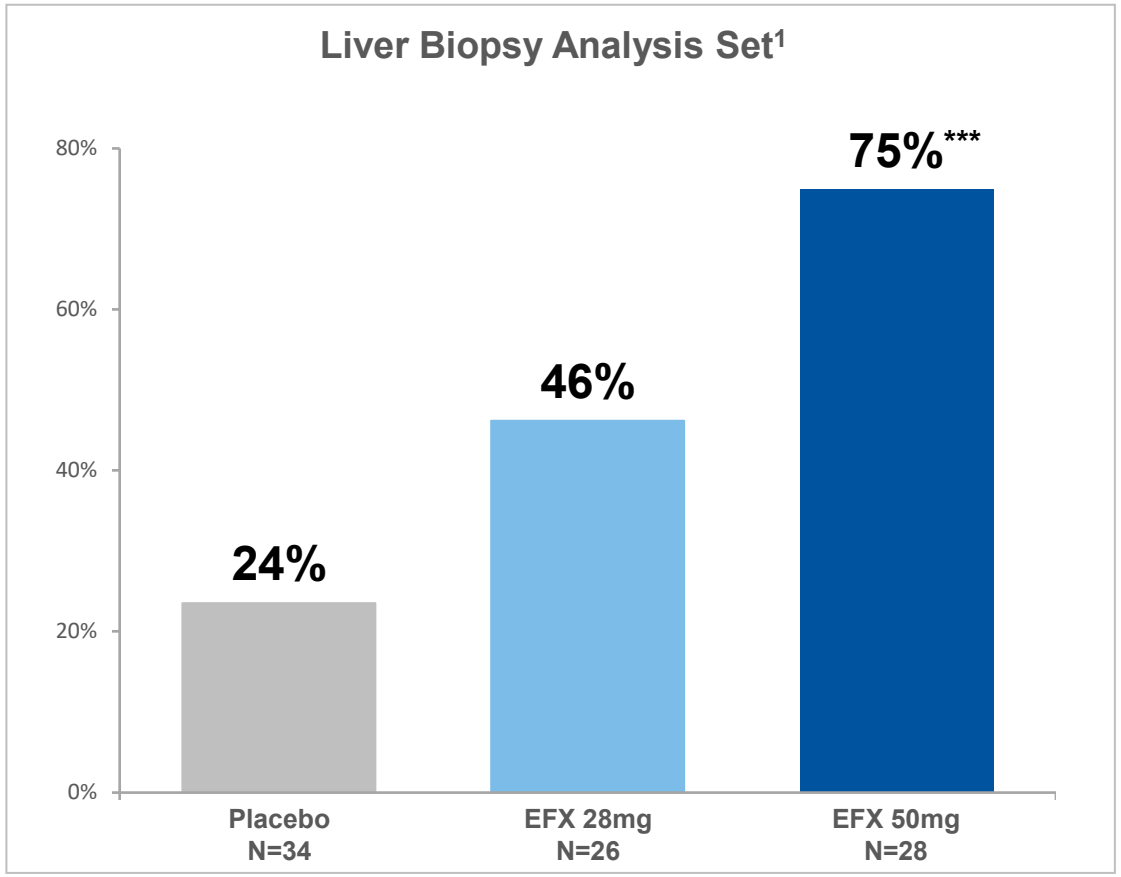
Parameter (Units), mean unless otherwise noted	Placebo (N=43)	EFX 28mg (N=42)	EFX 50mg (N=43)
Age (Years)	55	57	52
Sex (% Female)	63	69	53
Weight (kg)	108	104	103
Type 2 Diabetes (%)	65	76	70
PNPLA3 p.148 genotype[1] (% II / IM / MM)	32 / 34 / 34	26 / 54 / 21	16 / 63 / 21
Fibrosis Stage (F3), (%)[2]	70	64	63
NAFLD Activity Score (NAS)	5.4	5.1	5.6
Enhanced Liver Fibrosis (ELF) Score	9.8	9.7	9.8
Pro-C3[3] (µg/L) (GEN 2 ELISA)	125	113	145
Liver Stiffness by VCTE[4] (FibroScan) (kPa)	15	14	16
Hepatic Fat Fraction by MRI-PDFF[5] (%)	17.1	18.5	17.5
Alanine Aminotransferase (ALT) (U/L)	62	50	63
Aspartate Aminotransferase (AST) (U/L)	57	42	52
Proportion Treated with GLP-1 at Baseline (%)	21	18	9

[1] Among those with available genotype (88%, 93% and 88%), numbers may not add up to 100% due to rounding; [2] All patients either fibrosis stage 2 (F2) or stage 3 (F3); [3] Procollagen 3 N-Terminal Propeptide; [4] Vibration-controlled transient elastography; [5] Magnetic Resonance Imaging-Proton Density Fat Fraction

Source Data: Full Analysis Set (FAS)

Significant Anti-Fibrotic Effects for 50mg EFX at Week 96

Fibrosis Improvement ≥1 Stage & No Worsening of MASH at Week 96



[1] All subjects with baseline and Week 96 biopsies

*** p<0.001, versus placebo (Cochran-Mantel-Haenszel Test [CMH])

ITT Analysis[2]

Placebo (N=43)	EFX 28mg (N=40)	EFX 50mg (N=43)
19%	30%	49%**

[2] All missing biopsies are imputed as a non-responder

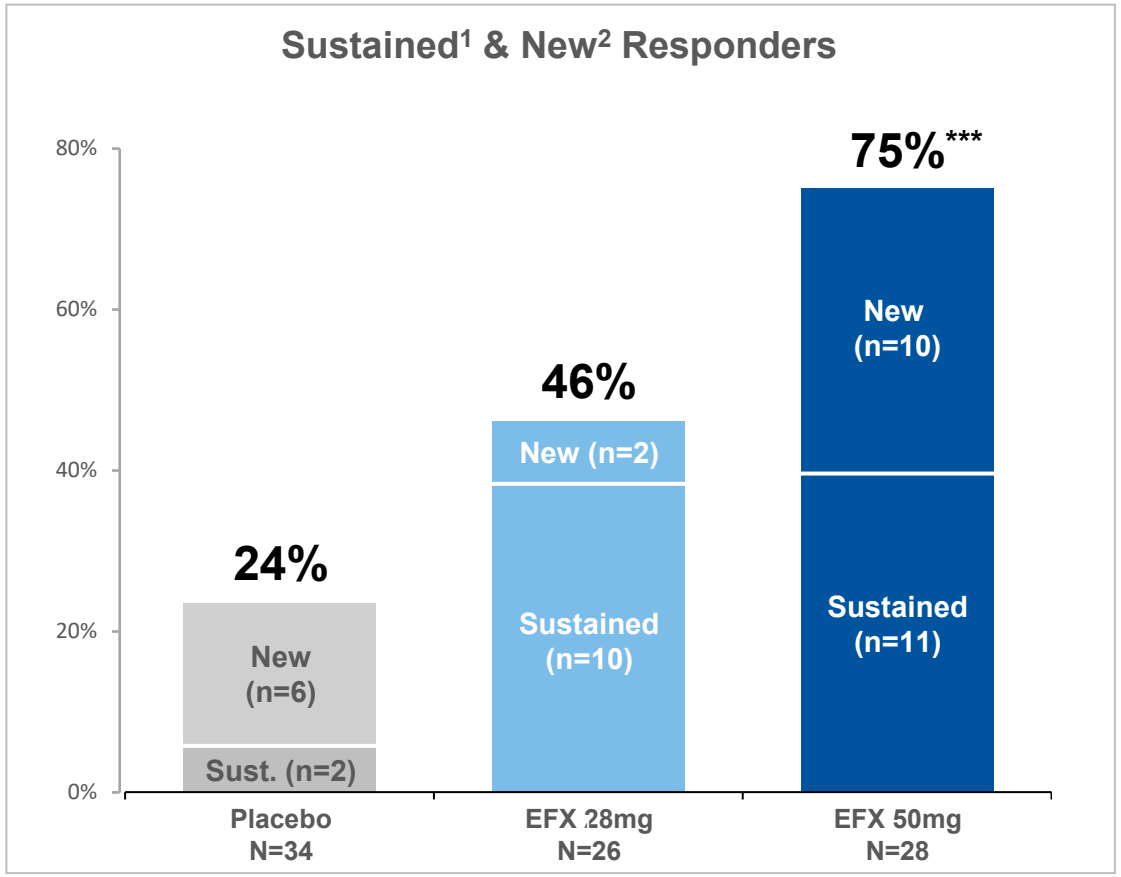
** p<0.01, versus placebo (CMH)

Biopsy Reading Method: Biopsies were independently scored by two NASH-CRN trained pathologists, blinded to subject, treatment, and sequence. A third pathologist was available to adjudicate in absence of consensus.

Source Data: Week 96 Liver Biopsy Analysis Set (LBAS-96); Modified Full Analysis Set (ITT)

Fibrosis Improvement Sustained from Week 24 to 96

Fibrosis Improvement ≥1 Stage & No Worsening of MASH at Week 96



[1] Responder at Weeks 24 & 96; [2] Responder at Week 96

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

Proportion of Week 24 Responders with Sustained Response at Week 96[3,4]

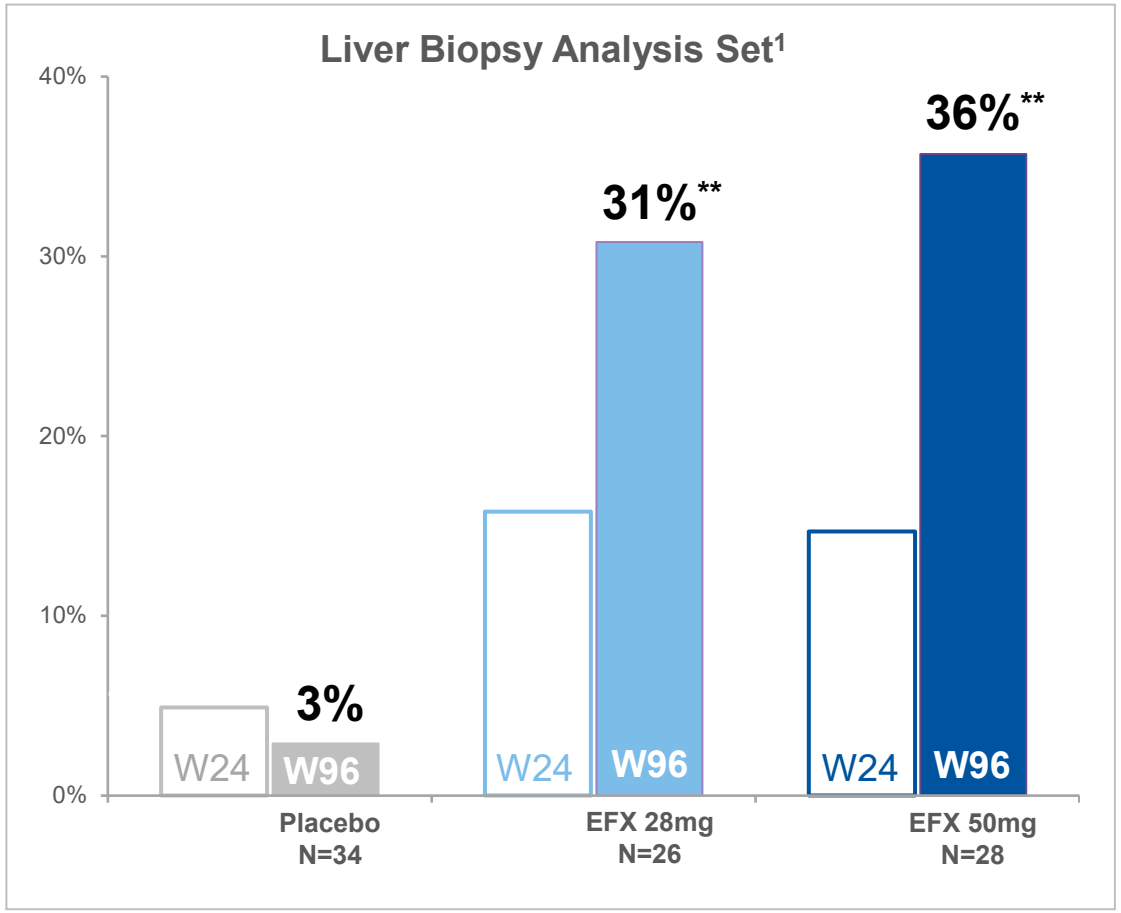
Placebo (N=5)	EFX 28mg (N=12)	EFX 50mg (N=12)
2 (40%)	10 (83%)	11 (92%)

[3] Among Week 24 responders with Week 96 biopsies
[4] Not analyzed for statistical significance

Source Data: LBAS-96

Rate of 2-Stage Fibrosis Improvement Doubled from Week 24 to 96

Fibrosis Improvement 2 Stages & No Worsening of MASH, Weeks 24 and 96



[1] All subjects with baseline and Week 24 or Week 96 biopsies

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

Week 96 ITT Analysis[2]

Placebo (N=43)	EFX 28mg (N=40)	EFX 50mg (N=43)
2%	20%**	23%**

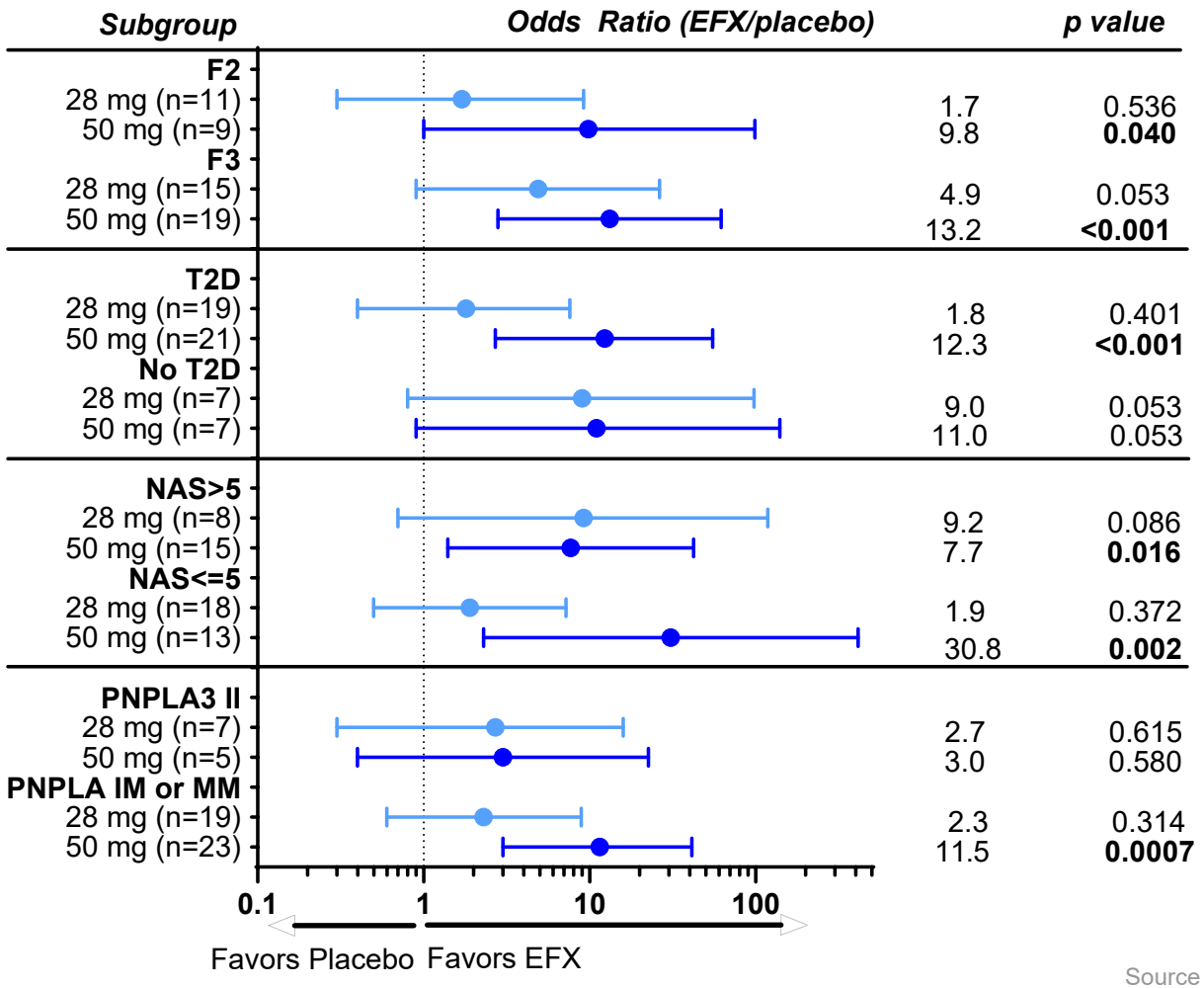
[2] Subjects with missing biopsies are imputed as non-responders

** p<0.01, versus placebo (CMH)

Source Data: LBAS-96; ITT

Consistent Response Across Subgroups

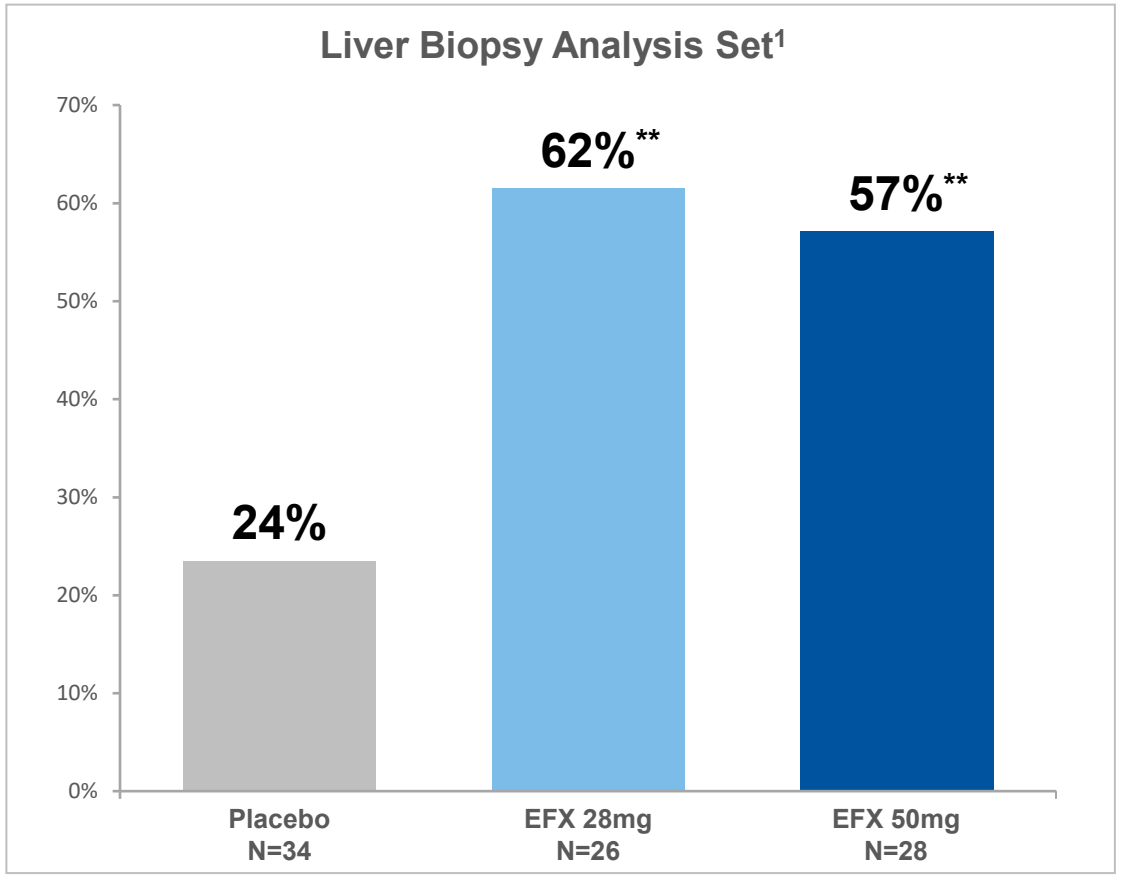
Fibrosis Improvement ≥1 Stage & No Worsening of MASH at Week 96



Source Data: Subgroups of LBAS-96 with available data
two-sided p value, Fisher's exact test (PNPLA3); CMH (all others)

Significant Rates of MASH Resolution Observed for Both EFX Doses at Week 96

MASH Resolution & No Worsening of Fibrosis at Week 96



[1] All subjects with baseline and Week 96 biopsies

** p<0.01, versus placebo (CMH)

ITT Analysis[2]

Placebo (N=43)	EFX 28mg (N=40)	EFX 50mg (N=43)
19%	40%*	37%*

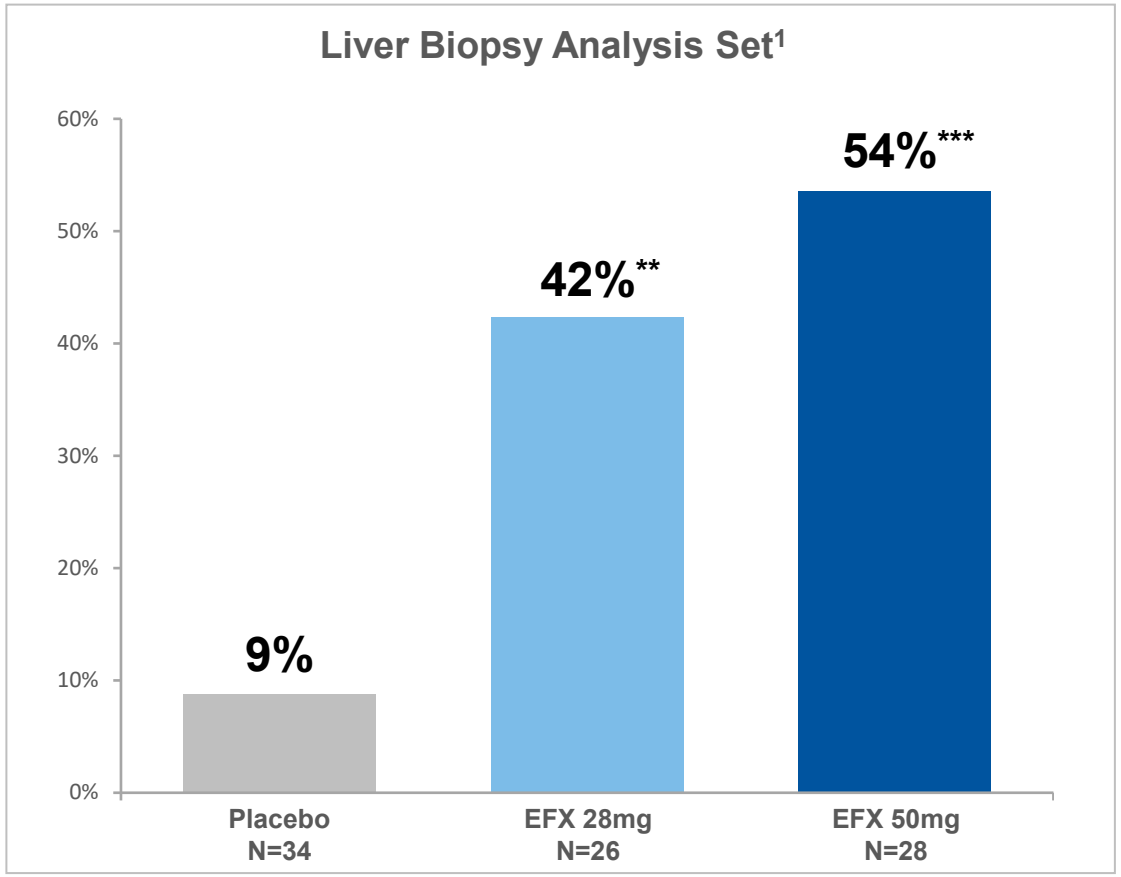
[2] Subjects with missing biopsies are imputed as non-responders

* p<0.05, versus placebo (CMH test)

Source Data: LBAS-96; ITT

Proportion of Patients who Improved Both Disease Activity and Fibrosis at Week 96

Fibrosis Improvement ≥1 Stage And Resolution of MASH at Week 96



[1] All subjects with baseline and Week 96 biopsies

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

ITT Analysis[2]

Placebo (N=43)	EFX 28mg (N=40)	EFX 50mg (N=43)
7%	28%**	35%**

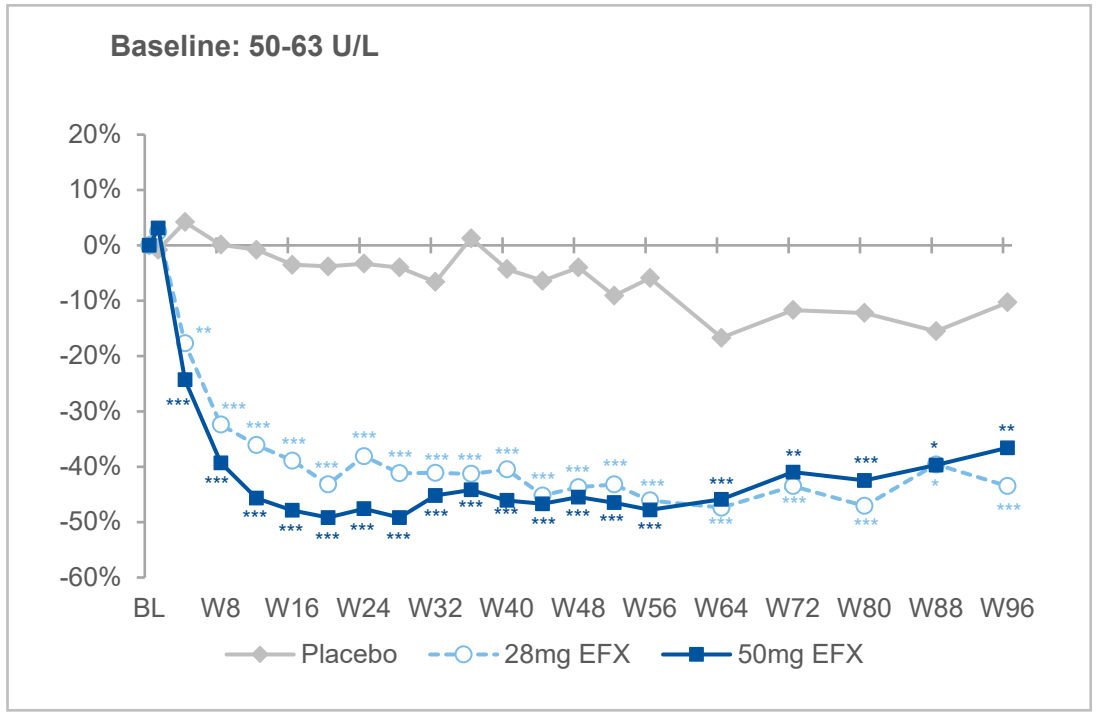
[2] Subjects with missing biopsies are imputed as non-responders

** p<0.01, versus placebo (CMH)

Source Data: LBAS-96; ITT

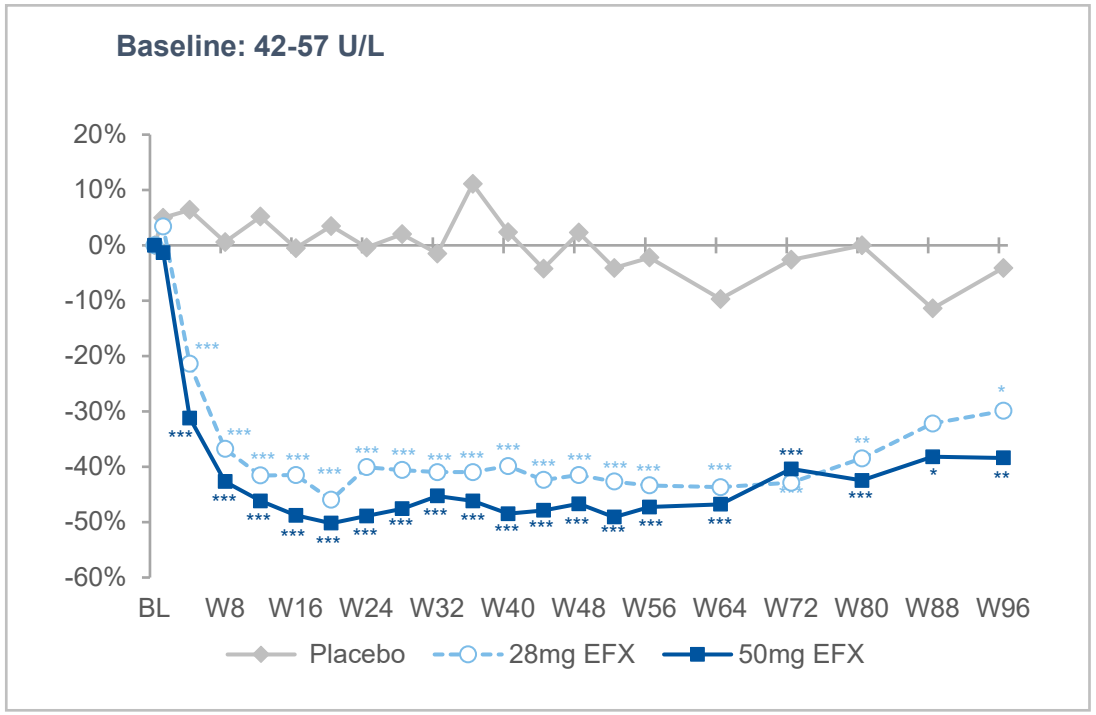
Significant Improvements in Markers of Liver Injury Sustained Through Week 96

ALT
LS Mean Percent Change from Baseline



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

AST
LS Mean Percent Change from Baseline

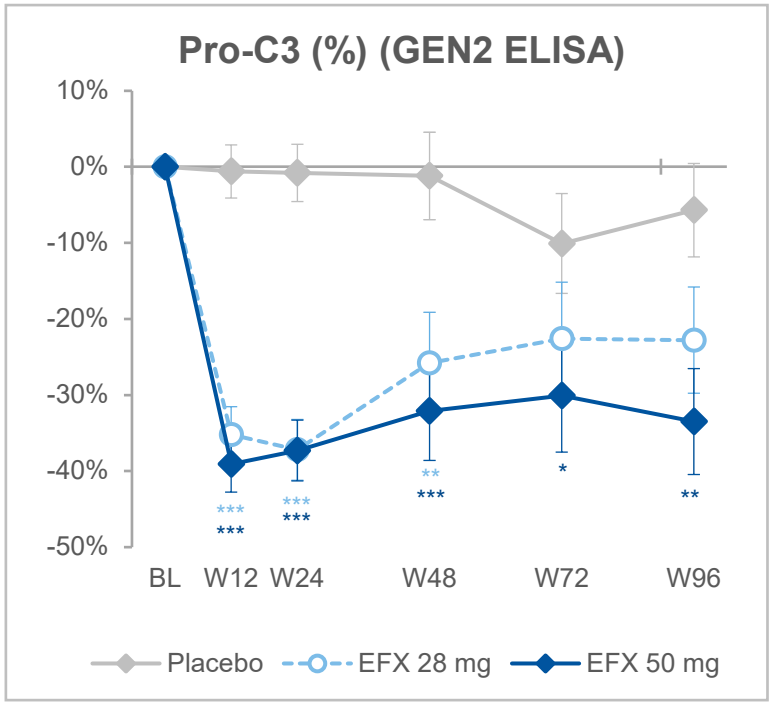


* p<0.05,** p<0.01, *** p<0.001, versus placebo (MMRM)

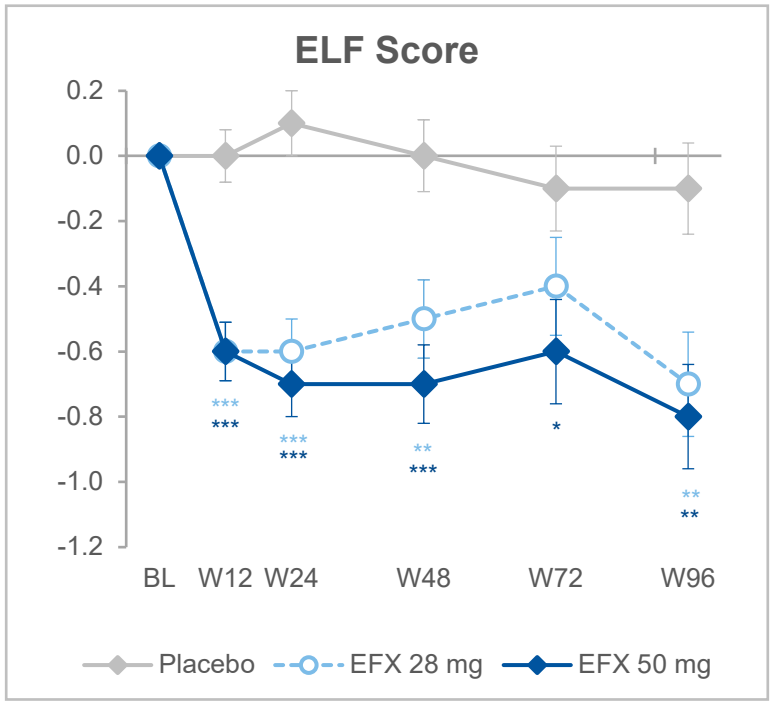
Source Data: FAS

Sustained, Significant Reductions in Non-Invasive Markers Corroborate Histological Improvement in Fibrosis

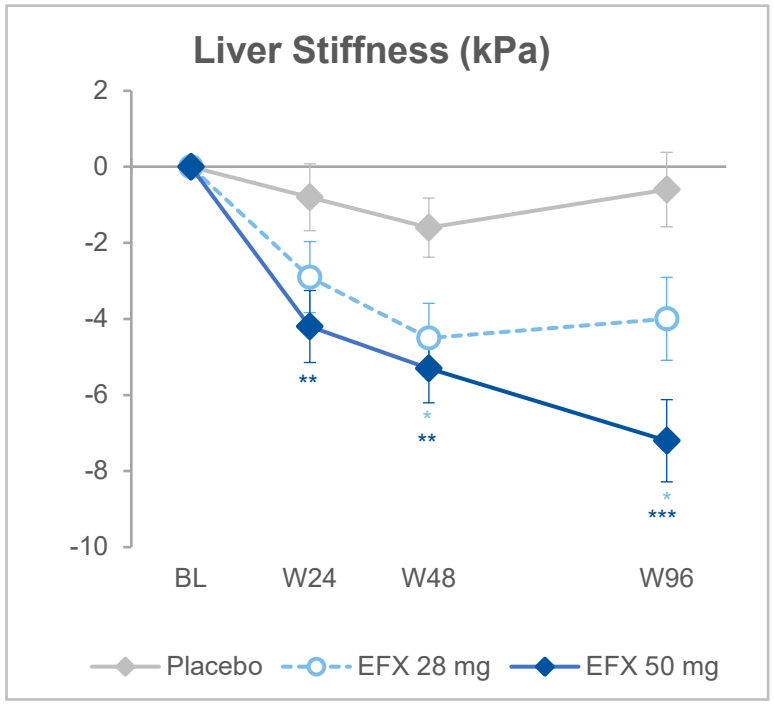
LS Mean Change From Baseline to Week 96



* p<0.05, ** p<0.01, *** p<0.001, versus placebo (Mixed Model Repeated Measures [MMRM])



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



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

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

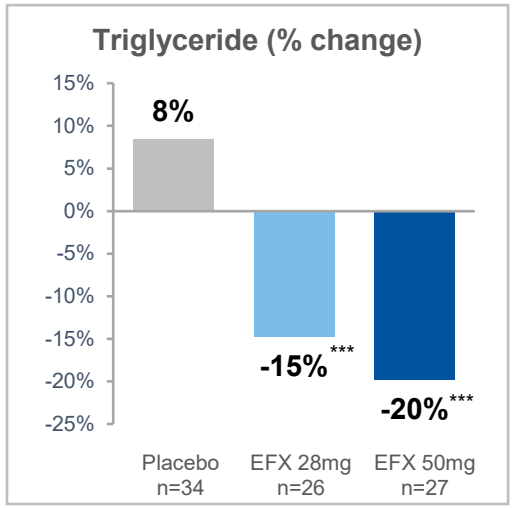
Treatment-Emergent Adverse Events (TEAE)
From Baseline through Week 96

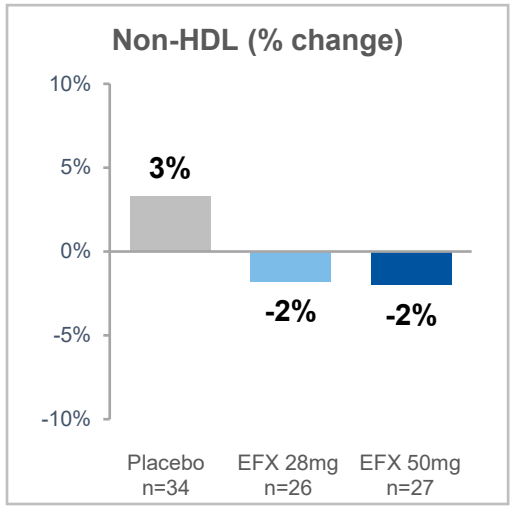
TEAE Overview	Placebo (N=43)	EFX 28mg (N=40)	EFX 50mg (N=43)
TEAE Leading to Death	0 (0%)	0 (0%)	0 (0%)
Treatment-Emergent Serious Adverse Events (SAEs)	4 (9%)	4 (10%)	7 (16%)
TEAE Leading to Discontinuation	0 (0%)	4 (10%)	5 (12%)

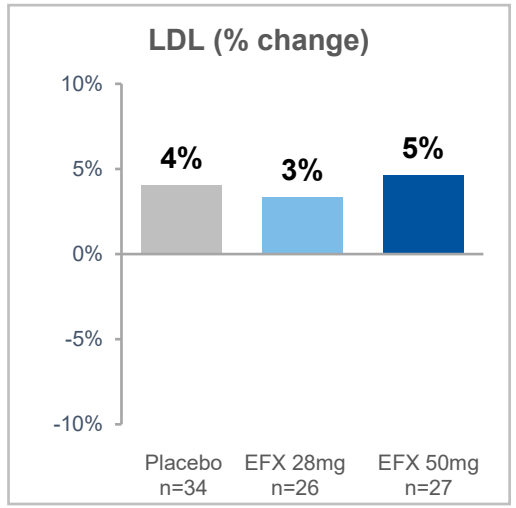
Most Frequent (≥15%) Drug–Related TEAEs	Placebo	EFX 28mg	EFX 50mg
Diarrhea	7 (16%)	16 (40%)	16 (37%)
Nausea	5 (12%)	12 (30%)	14 (33%)
Increased Appetite	3 (7%)	7 (18%)	10 (23%)
Injection Site Erythema	6 (14%)	8 (20%)	7 (16%)
Injection Site Bruising	2 (5%)	6 (15%)	3 (7%)

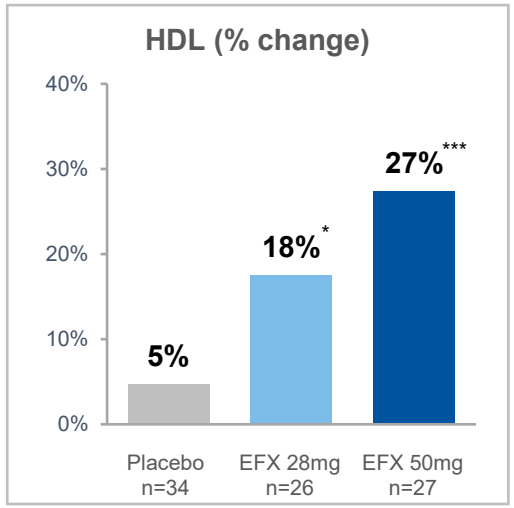
Source Data: Safety Set

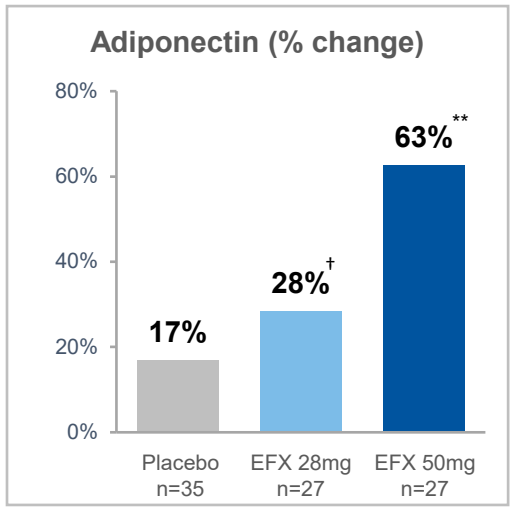
Improvement in Lipoproteins, Markers of Insulin Sensitivity and Body Weight After 96 Weeks, LS Mean Change From Baseline

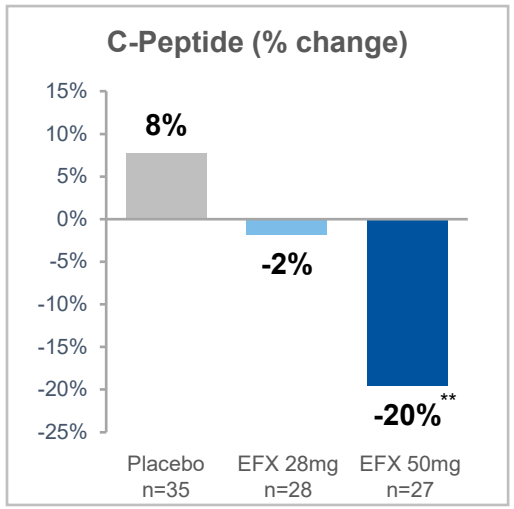


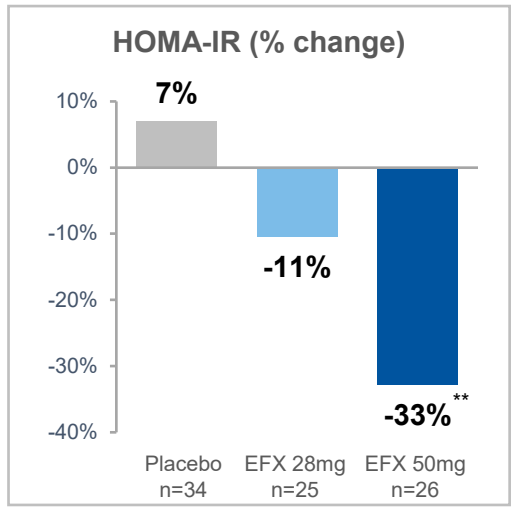


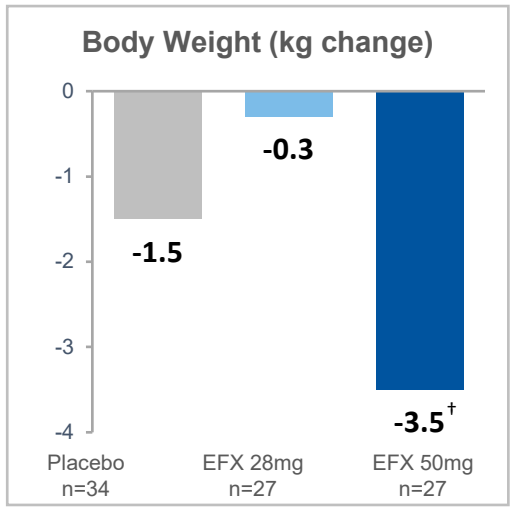












* p<0.05, ** p<0.01, *** p<0.001, versus placebo (MMRM); † p<0.05, versus baseline (MMRM)

Source Data: FAS, non-missing values only, no imputation

Safety Overview

- Markers of liver function and hemostasis remained stable, including MELD, and CP score
- No reported events of DILI
- Blood pressure unchanged after 96 weeks of EFX Treatment
- No significant changes in BMD after 48 weeks
- Statistically significant, modest reductions in BMD after 96 weeks, but clinical relevance remains to be determined

Conclusion:
Unprecedented Antifibrotic Activity Observed for EFX after 96 weeks

- Early fibrosis response at week 24 sustained and expanded to week 96
- 1 in 3 subjects experienced 2-stage improvement in fibrosis
- Half of subjects experienced fibrosis improvement and MASH resolution
- Histologic improvements corroborated by non-invasive markers
- Improvements in metabolic health largely maintained through 96 weeks
- Acceptable safety and tolerability profile, with mostly mild-to-moderate GI events

Acknowledgements

Thank you to the patients and their families, as well as the investigators and their teams, who have participated in the completed HARMONY study.

Investigators: *Gary Abrams, MD • Naim Alkhouri, MD • Rafael Amaro, MD • Christian Andrade, MD • Robert Barish, MD • Shekhar Challa, MD • Andrew deLemos, MD • Michael Fine, MD • Juan Frias, MD • Michael Fuchs, MD • Sudhanshu Gogia, MD • Stephen Harrison, MD • Paul Hellstern, MD • Robert Herring, MD • Robert Jenders, MD • Arun Khazanchi, MD • Anita Kohli, MD• Donald Lazas, MD • Mark Leibowitz, MD • Kathryn Lucas, MD• Fernando Membreno, MD • Apurva Modi, MD • Ann Moore, NP • Robert Morin Jr., MD • Abdullah Mubarak, MD • Guy Neff, MD • Mazen Noureddin, MD • Grisell Ortiz-Lasanta, MD • Rashmee Patil, MD • Robert Rahimi, MD • Gary Reiss, MD • Peter Ruane, MD • William Sanchez, MD • Aasim Sheikh, MD • Muhammad Sheikh, MD • Elliot Shin, MD • Mohammad Siddiqui, MD • Scott Wofford, MD • Cynthia Wright, MD • Ju Dong Yang, MD*